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LEUCOPLAKIA OF THE VULVA*

Preliminary Report

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GYNECOLOGISTS, dermatologists and most experienced physicians have long recognized as a clinical entity the vulvar lesion characterized by grayish white patchy thickening, fissuring, edema, and areas of atrophy. Yet, the etiology of this troublesome lesion is unknown, its clinical course is obscure, the histologic picture controversial, and a satisfactory treatment wanting. Indeed, there is not even complete agreement among physicians as to what the condition should be called. Brewer[1] gleaned 18 different names from the literature, none of which has received universal approbation. It may not matter much just what this entity is called, but there should be agreement on a suitable and appropriate term. For a somewhat similar condition occurring in the mouth Schwimmer,[4] in 1877, coined the word "leucoplakia." Taussig,[2] in this country, fostered use of this term for the vulvar lesion. Since the condition generally is characterized by an easily visualized grayish white patchy thickening frequently associated with fissuring, edema, and later with atrophy, and, since the disease is by no means confined to postmenopausal women, we prefer the term leucoplakia. In this report the term is used in its broad sense to include both the hypertrophic as well as an atrophic (kraurosis) phase of the disease.

Our interest in leucoplakia stems from two sources: first, an increasing awareness of the numerous shortcomings in our concept of the disease and its treatment. We recognize many of its characteristics, but, like so many pieces of a jigsaw puzzle, we do not know how they all fit together. Second, leucoplakia appears to have considerable cancer potentiality and for this reason

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should serve as a fruitful field for studying early development, rate of growth, and similar aspects of squamous cell carcinoma.

Since July, 1931, 153 patients with leucoplakia of the vulva have been processed through the University of Michigan Hospital. Of these, 143 were seen prior to July, 1945, and were treated in the customary manner with everything from soothing lotions to surgery. These we shall call our *prestudy* group in contradistinction to a *study* group of 36 patients subjected to careful scrutiny and observation since Jan. 1, 1946. This study group includes 25 patients from the prestudy category and 11 new patients first seen during 1946.

The average age for the 143 patients in our prestudy group was 55.6 years. The eldest was 80 and the youngest 23 years. That leucoplakia is not exclusively a disease of the aged is shown by the fact that one of our patients was aged 30 years, and two were 23 years of age. One of the latter was pregnant. Green-Armytage[5] reported a case of advanced leucoplakia in a pregnant woman aged 42 years. He also mentioned four other instances occurring during pregnancy. Klaften[6] reported leucoplakia and subsequent kraurosis in a 6-year-old child. The diagnosis was confirmed by biopsy. Ketron and Ellis[7] noted vulvar changes in an 8-year-old child which they temporarily classified as leucoplakia.

Rigby[8] states that leucoplakia is uncommon in the Negro race. De Lima Filho[19] listed one Negro woman in his series. There were no Negro patients in our series.

The marriage and parity status among our 143 *prestudy* patients are shown in Tables I and II.

TABLE I. MARITAL STATUS

Married	97	67.7%
Widowed	37	25.8%
Divorced	1	0.7%
Single	7	4.9%
Status unknown	1	0.7%
	143	100.0%

TABLE II. PARITY

Parous	97	67.7%
Nulliparous	30	20.9%
Parity unknown	16	11.1%
	143	99.7%

One hundred fourteen, or 78.5 per cent, of the 143 patients were post menopausal. In 10 the menopause had been artificially induced.

The symptoms complained of are shown in Table III. The average duration of results obtained in the prestudy group.

Thirty-three, or 23.1 per cent, had an associated carcinoma presumably on a leucoplakic basis. This incidence is less than half the commonly cited 50 per cent noted by Taussig.

Treatment for the prestudy group included a variety of empirical therapy and excision or vulvectomy in 54 cases. There were 13 recurrences (24.7 per

TABLE III. SYMPTOMS

Pruritis	108
Irritation and burning	31
Vaginal discharge	20
Pain and burning on urination	11
Pruritus ani	9
Ulcers	8
Pain in vulva	8
Bleeding	6
Dyspareunia	2

TABLE IV. RESULTS OF TREATMENT IN PRESTUDY GROUP

Unimproved	21	14.6%
Moderate improvement	25	17.4%
Greatly improved	26	18.1%
Died	16	11.1%
No follow-up	55	38.3%
	143	99.5%

cent) among the surgically treated patients. Table IV gives a rough evaluation of results obtained in the *prestudy* group.

These results should not be interpreted optimistically. Experience has shown that improvement is frequently temporary. Furthermore, the results shown in Table IV do not reflect the heartache and discomfort suffered by these patients with each succeeding therapeutic failure or as a result of genital contraction following vulvectomy. Neither does it portray the futility felt by the physician in his search for a cause and cure.

Our planned study of leucoplakia began in January, 1946. Since then 36 patients (11 new and 25 return cases) have been processed according to the schedule shown in Table V. For a variety of reasons it was not possible to achieve the full prescribed study for every patient. Such data as were obtained form the basis for the remainder of this report. In developing this program of study it was hoped that we might:

a. Investigate many of the frequently voiced but inadequately studied causative factors. By so doing we hope to clear the way for further study regarding etiology later on. This preliminary report is largely a summation of this phase of our work.

b. Contribute toward a better understanding of the clinical course of leucoplakia.

c. Gain a clearer picture of its histopathology through study of repeat biopsy material.

d. Improve our treatment.

e. Evaluate more accurately its precancerous potentialities.

While our experience with leucoplakia of the vulva has been extensive, it did not become intensive until 1946. We have purposely avoided becoming wedded to any fixed concept of the disease beyond that which has been necessary to serve as a common meeting point for discussion. We recognize the clinical characteristics and the various histologic pictures presented by advanced leucoplakia of the vulva. We are also familiar with the clinical and

histologic appearance of the atrophy so well described by Montgomery, Counsellor, and Craig[10] and best known under the term kraurosis. Since these two conditions not uncommonly occur as associated lesions in the same patient, the possibility of a transitional phase seems logical. Just which direction the transition goes, however, is still a controversial matter. Taussig seemed convinced that the changes generally grouped under the term hypertrophic preceded those of atrophy. Terrhun,[9] on the other hand, took the contrary view, and with this Brewer[1] appears to agree. Cinberg[3] does not recognize kraurosis as a disease entity. The picture is further confused by the trauma from scratching or rubbing, secondary infection, and such conditions as Lichen Planus which presents a histologic picture not unlike that seen in leucoplakia. (Figs. 1 to 9.*) Perhaps as we continue to observe the individual patients in our series and repeatedly biopsy the lesion we may crystallize the true course of events in leucoplakia of the vulva.

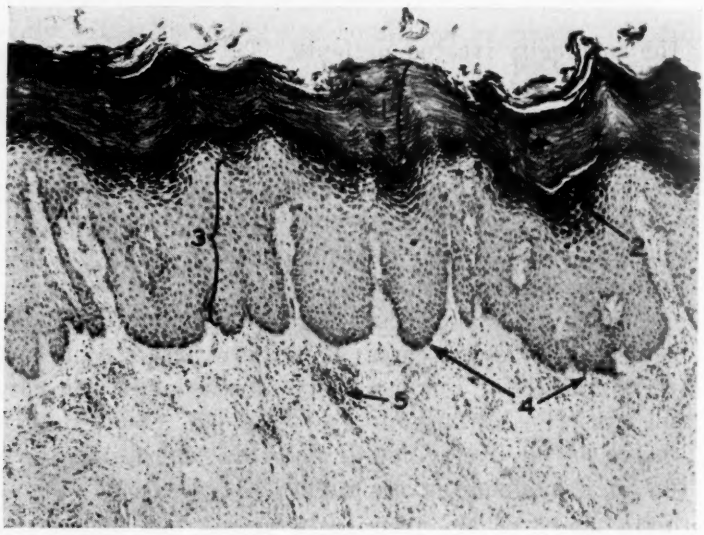

Fig. 1.—Hypertrophic leucoplakia. (1). Stratum corneum showing marked hypertrophy (hyperkeratosis). (2). Stratum granulosum showing a marked increase in the normal number of cell layers. Note the increase or capping effect over the rete pegs. (3). Stratum spinosum or prickle cell layer showing marked hyperplasia with elongation and widening of the rete pegs (acanthosis). (4). Stratum germinativum or basal layer showing enlargement of the cells with an increase in their grouping over the tips of the rete pegs. Liquefaction necrosis not yet remarkable. (5). Early cellular infiltration in the dermis.

Since the average age of women with leucoplakia of the vulva is 55 years, it is not surprising that a reasonable number should present other evidence of organic disease. A list of coexisting disease in our study group of 36 patients is shown in Table VI.

Some of the 36 patients had more than one co-existing organic disease. We are not impressed by any apparent relationship to the vulvar lesion. There were no diabetics in our study group.

The blood pressure determinations were not remarkable. Nine patients revealed a pressure of 150/90 or over.

*The tissue sections and photomicrographs were prepared and are presented through the courtesy of the Department of Pathology and Photography of the University of Michigan Hospital.

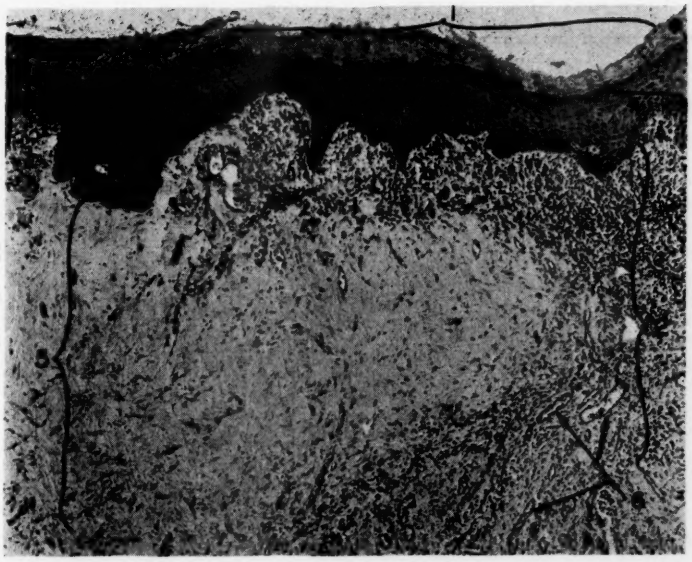

Fig. 2.—Transitional type of leucoplakia (leucokraurosis). (1). The stratum corneum included in this bracket shows parakeratosis (retention of the surface cell nuclei) with some edema and loss of lamination. The granular layer is partially absent in this segment, indicating rapid proliferation of the epidermal cells. (2). The dermis at the right is heavily infiltrated with lymphocytes. (3). Hyperkeratosis of stratum corneum. (4). Moderate acanthosis throughout the stratum spinosum. (5). The dermis at the left reveals a marked collagenous degeneration which extends more than two-thirds across the section. Note the blood vessels in this area have been almost entirely obliterated. (6). Dilated blood vessels at the margins of the areas of active infiltration. (7). The basal layer in this area shows edema and loss of palisading with patchy liquefaction necrosis.

Fig. 3.—Moderately far-advanced atrophic leucoplakia (kraurosis). (1). Hyperkeratotic stratum corneum. (2). The stratum granulosum is easily made out though patchy in areas. (3). The prickle cell layer is atrophic. Practically all evidence of the rete pegs has disappeared, having been compressed by changes in the upper dermis. Note: The basal cell layer is fragmented and irregular having lost the orderly palisade appearance of normal germinal cells. This is due to liquefaction necrosis and intercellular edema. (4). The upper portion of the dermis has undergone hyaline and collagenous degeneration. (5). The middermis shows a moderately diffuse cellular infiltration. (6). The lower dermis shows very little change other than some increase in fibrosis. (7). A keratotic plug in an epidermal orifice.

TABLE V. LEUCOPLAKIA DATA SHEET

UNIVERSITY OF MICHIGAN HOSPITAL
Department
of
Obstetrics and Gynecology

Name_____ Age_____ Hospital Number_____
Address _____
Marital Status_____ Parity_____ Race_____ Series Number_____

1. History									
2. Physical examination									
3. Dermatology reference									
4. Allergy reference									
5. Psychiatry reference									
6. Medical reference									
7. Oral surgery reference									
8. Urinalysis									
9. Blood study									
10. Blood ascorbic acid									
11. Blood vitamin A									
12. Gastric analysis									
13. Biopsy									
14. Vaginal smears									
15. 17 Ketosteroids									
16. Estrogen assay									
17. Gonadotropins (F.S.H.)									
18. Culture (bacterial)									
19. Yeast culture									
20. Photograph									
21. _____									
22. _____									

TABLE VI. COEXISTING ORGANIC DISEASE

Hypertension	9
Obesity	8
Organic heart disease	5
Arthritis	5
Secondary anemia	4
Pernicious anemia	2
Generalized arteriosclerosis	2
Pelvic relaxation	3
Menopausal bleeding	2
Cervical polyp	1
Uterine fibroids	1
Asthma	1
Varicosities of legs	1
Tuberculosis (arrested)	1
Hypothyroidism	1
Chorioretinitis	1
Spina bifida occulta	1
Normal healthy women without associated disease	7
Pregnancy	1

Blood serology was negative in all but one instance. De Lima[19] considered syphilis a strong predisposing factor.

Urinalyses were negative in all but four patients. One of these was found to have occasional glycosuria, while three others showed evidence of urinary tract infection.

Twenty-four patients had complete blood studies. Of this number 8 (33.3 per cent) were reported as normal by the hematologist. Ten (41.6 per cent) showed evidence of infection as indicated by increased sedimentation rate,

toxic granulations, or an increased white count. The fact that 41.6 per cent revealed evidence of infection is interesting in view of the inflammatory infiltration seen in the dermis in leucoplakia. Since 50 per cent of the patients studied showed no evidence of infection in the blood picture it is probably safe to assume that the changes noted were due to infection elsewhere in the body. Two of the 24 patients having complete study demonstrated the picture of pernicious anemia and two revealed idiopathic hypochromic anemia, a

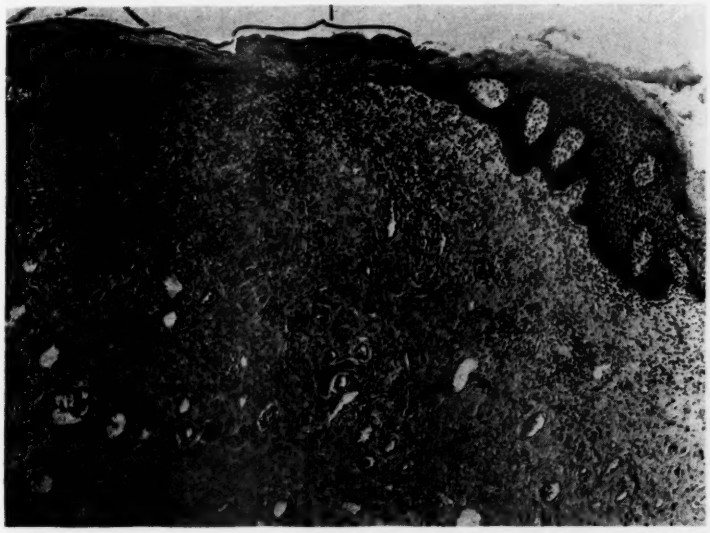

Fig. 4.—Leucoplakia showing fissuring. (1). Area of fissure showing some secondary infection and granulation tissue. There is marked cellular infiltration throughout the section. (2). Numerous dilated vessels of the dermis, part of the granulation tissue.

Fig. 5.—Leucoplakia showing dermal edema and early collagenous change. (1). Only slight hyperkeratosis. (2). There is still evidence of acanthosis. The rete pegs are compressed and show atrophy. (3). The upper dermis shows marked edema which has replaced the cellular infiltration and the blood vessels of the area. (4). Lower dermis showing moderate evidence of cellular infiltration.

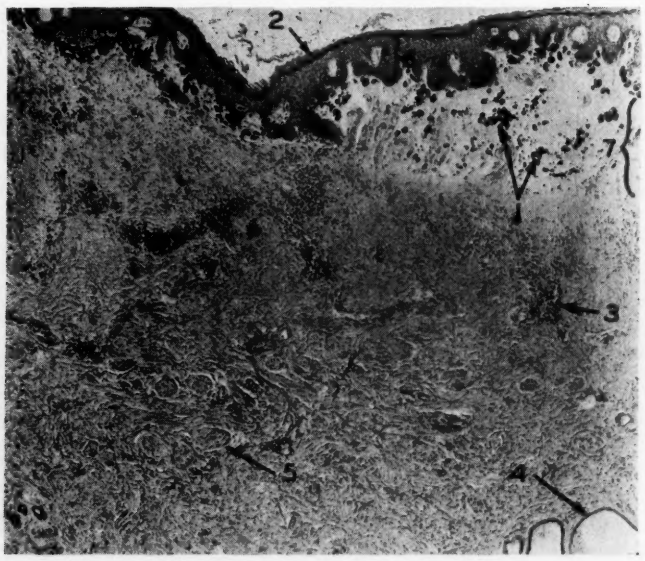

Fig. 6.—Transitional leucoplakia showing phagocytized melanin pigment. (1). Along the superficial dermis pigment is seen. Hyaline tissue degeneration adjacent to these melanin agglutinations probably accounts for its being held in this location. The melanin originated in melanoblasts of the basal cell layer but was liberated by liquefaction necrosis of that layer, and later phagocytized and trapped in the homogenized tissue of the superficial dermis. (2). Stratum corneum shows little or no hyperkeratosis. (3). Focal lymphocytic infiltrations. (4). Dilated apocrine sweat gland. (5). Smooth muscle bundle. (6). Acanthosis with elongation of the rete pegs which are being compressed by the underlying, dermal, hyalin changes. (7). Edema and hyaline, collagenous degeneration in the superficial dermis.

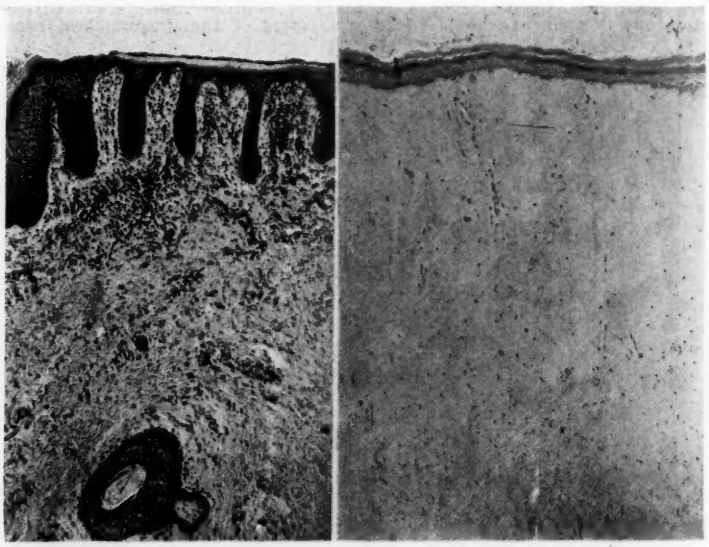

Fig. 7.—Tissue sections taken from a partial vulvectomy. These show a marked contrast from a hypertrophic leucoplakia on the left to a far-advanced atrophic leucoplakia (kraurosis) on the right, occurring simultaneously in the same patient.

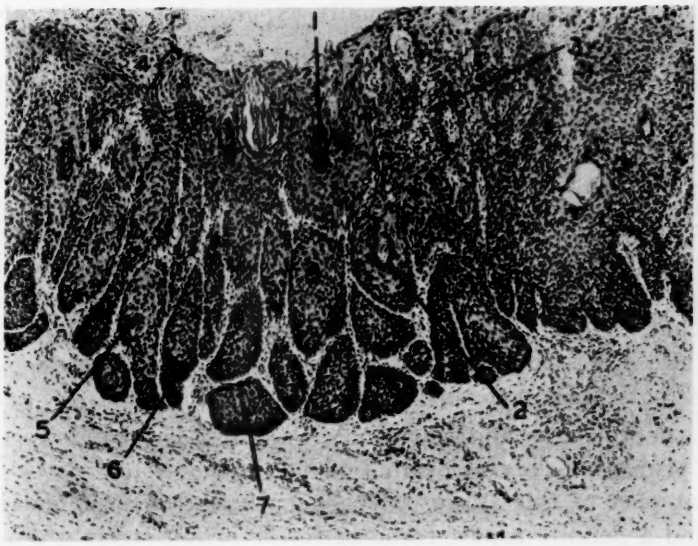

Fig. 8.—Intraepidermoid carcinoma developing in leucoplakia. This type of lesion has all the characteristics of Bowen's disease and must be judged by the same criteria. These are listed: (Lee McCarthy, Histopathology of Skin Diseases, St. Louis, 1931, The C. V. Mosby Co., p. 452). (a). Hypertrophic epithelium with dyskeratosis. (Faulty development of the epidermis in which the prickle cells undergo abnormal, premature or imperfect keratinization). (b). Preponderance of intracellular edema over intercellular edema. (c). Numerous mitotic figures. (d). Clumping of large cells with giant nuclei. (e). Hyper- and parakeratosis of the stratum corneum with invagination through the stratum granulosum. (f). General confused appearance of the basal layer.

In reference to Fig. 8: (1). Invagination of the stratum corneum through the stratum granulosum. (2). A keratin plug deep within the prickle cell layer. (3). Area showing marked intracellular edema. (4). Stratum corneum showing marked hyper- and parakeratosis. (5). Prickle cells deep within hyperplastic epithelium and showing loss of polarity, premature keratinization and a tendency to form intraepidermal pearl configurations. (6). Loss of polarity of the basal cell layer. (7). Within this area are few large cells with large nuclei. Mitotic figures cannot be made out at this magnification.

Fig. 9.—Carcinoma developing in an atrophic leucoplakia (kraurosis). (1). Atrophic epithelium showing an atypical arrangement of the cells. (2). Keratohyalin mass below the epithelium surrounded by carcinoma cells. This is a cornifiying squamous cell carcinoma. (3). Inflammatory cellular infiltration. (4). Carcinomatous downgrowth with small keratohyaline plugs. (5). Small nests of carcinoma cells. (6). Collagenous tissue of the dermis which is one morphologic feature of atrophic leucoplakia (kraurosis).

higher incidence than we would normally expect. Minor blood abnormalities were noted in two patients.

Study of the vaginal secretions showed only one patient with active trichimonas vaginalis vaginitis.

Yeast cultures were positive in five, but clinical evidence of yeast infection was not evident in any of these five individuals.

Twenty-six of the 36 patients in our study group were examined by a dermatologist. In 21 instances he concurred in the diagnosis of leucoplakia. In three his diagnosis was Lichen Simplex or Lichen Planus, but two of these had what histologically and gynecologically was considered to be leucoplakia. In two others his diagnosis was neurodermatitis and monilia vulvitis. Both of these patients had the histopathology of leucoplakia.

Because nervousness and emotional instability is frequently noted in patients with pruritis, a careful evaluation of the emotional status was deemed an important part of this study. Consequently, psychiatric consultation was requested and a definite report received for 32 of our study group. The findings are grouped as follows:

TABLE VII. PSYCHIATRIC CONSULTATIONS

Definite contributory psychoneurotic background	7	21.3%
Some emotional instability but of questionable significance	13	40.6%
No evidence of any psychoneurotic contributing factor	11	34.4%
Organic brain disease	1	3.1%
	32	99.4 %

The possibility of a conversion type psychoneurosis predisposing to the development of a chronic irritative vulvar lesion has long been suspected. Emotional instability is likely to be a factor in aggravating and prolonging the pruritic phase of the disease, but we cannot yet assume a cause and effect relationship. Future contributions on this aspect of the disease should be of considerable interest.

Parks[11] emphasized the similarity between certain oral and vulvar lesions. Fourteen of our patients were examined by oral surgeons. One revealed two small patches presumably of leucoplakic character and four showed either gingivitis or stomatitis. Chronic irritation is thought to be a factor in leucoplakia of the mouth; and, we have given considerable thought to irritation, such as trauma from rubbing or scratching, as a causative factor in vulvar leucoplakia, but we have not yet been able to evaluate its role as an etiologic factor.

Twenty-five of our group were studied with reference to allergic manifestations. Fourteen, or 56 per cent, had no allergic history or recognizable sensitivity. Eleven, or 44 per cent, revealed an allergic background of variable severity, and in two the pruritis was somewhat relieved after removal of the offending allergen.

Because of the hyperkeratoses noted in vitamin A deficiency the possibility of leucoplakia being a nutritional disease has been of more than casual

interest. Swift[12] described a series of patients with vulvar changes which he attributed to vitamin A deficiency. In Swift's opinion the difficulty was not due to an absence of vitamin A but rather, to a lack of hydrochloric acid in the stomach, which he claimed, resulted in failure of utilization of vitamin A. Since pruritus vulvae on a leucoplakic basis is not a particularly common symptom among women with pernicious anemia in whom an achlorhydria is a constant finding this cause and effect relationship does not seem to be borne out in fact. Nevertheless, the possibility of a vitamin A deficiency playing an etiologic role is intriguing. In order to check on this, blood vitamin A determinations were made on 10 patients in our study group and in only one instance was the level below limits accepted as normal (Table VIII). All blood vitamin A determinations were according to the colorimetric method of Dann and Evelyn[13] using antimony trichloride as the color reagent.

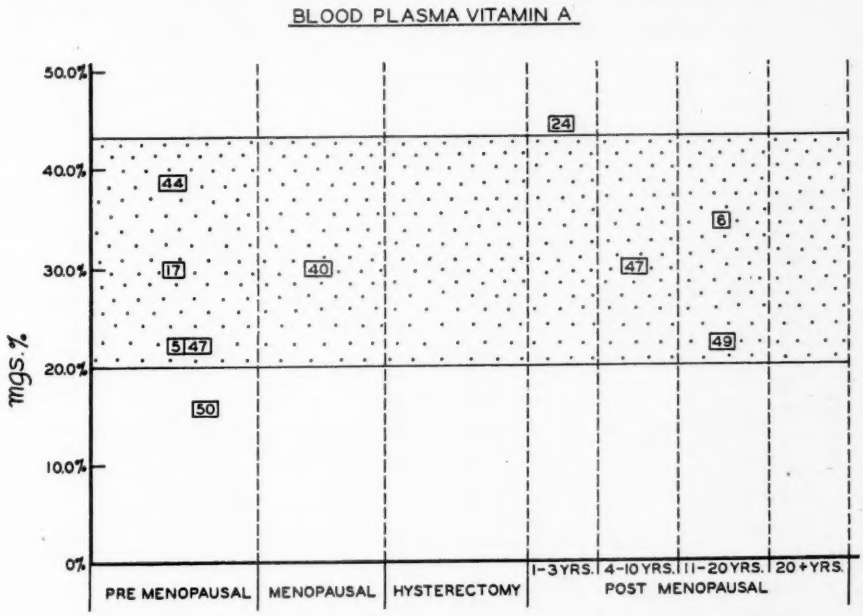

Table VIII.

The gastric acidity was noted in 12 patients. Six revealed free hydrochloric acid and six had no free acid (Table IX). Two of the later were pernicious anemia patients. An achlorhydria is not found in healthy individuals, although it has been stated[18] that 25 per cent of the general population over 65 years of age have no free hydrochloric acid. While the number of acid determinations in our study is not yet large enough to be of significance, the fact that many patients with leucoplakia are elderly, and one-half of the women in our series on whom the test was made did have free hydrochloric acid would seem to minimize any important relationship. Furthermore, three of the six patients with an achlorhydria had a normal or high vitamin A blood level.

Blood plasma ascorbic acid levels were determined for 22 patients. The results are shown in Table X. In 14, or 63.6 per cent, the levels were normal or above. Most of the ascorbic acid determinations were by the titration method of Farmer and Abt[14] employing the indicator 2-6 dichloraphenolindophenol. In a few patients ascorbic acid levels were determined by the colorimetric method of Roe and Kuether.[15]

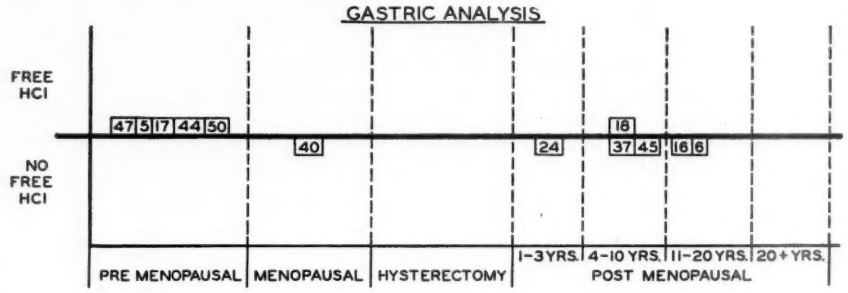

Table IX.

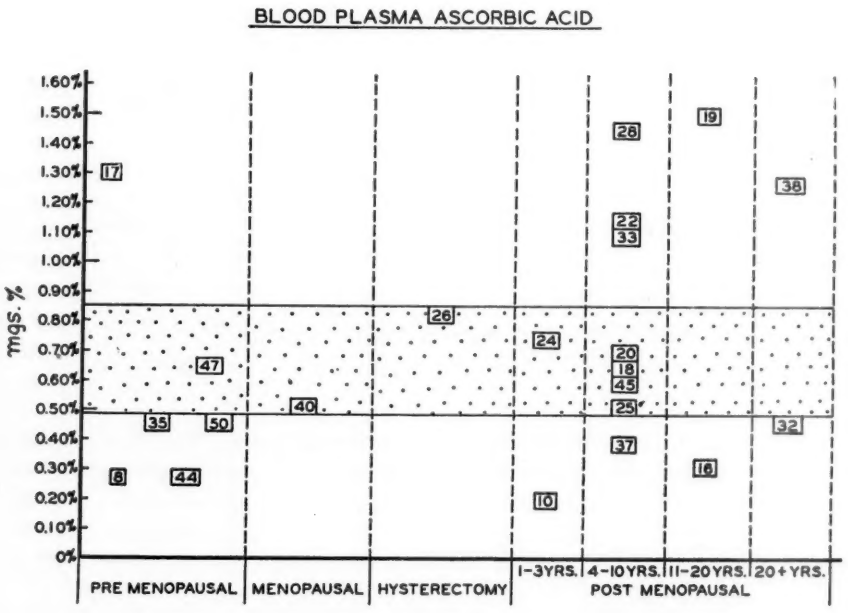

Table X.

The concept that leucoplakia is associated with an estrogen deficiency has been rather widely accepted. Most textbooks on gynecology name estrogen deficiency as an etiologic factor. That this seems unlikely is borne out by our studies and is further supported by the fact that leucoplakia may exist without improvement in young women during pregnancy when the estrogen levels are normally high. Table XI shows the results of urinary estrogen assay on 26 patients in our study group. Twenty-two, or 84 per cent, had normal or above normal estrogen excretion rates. All urinary estrogens were extracted by the method of Gallagher and Koch.[16] The procedure consisting of separate

acid hydrolysis, extraction with benzene, and subsequent separation of estrogens from androgens and 17-ketosteroids with sodium hydroxide. The estrogen fraction was assayed by the biologic method of Allen and Doisy[17] based on the response of the vaginal epithelium of the spayed rat.

Because of the present-day interest in the 17-ketosteroids, these determinations were made on 26 of our study group. The results are shown in Table XII.

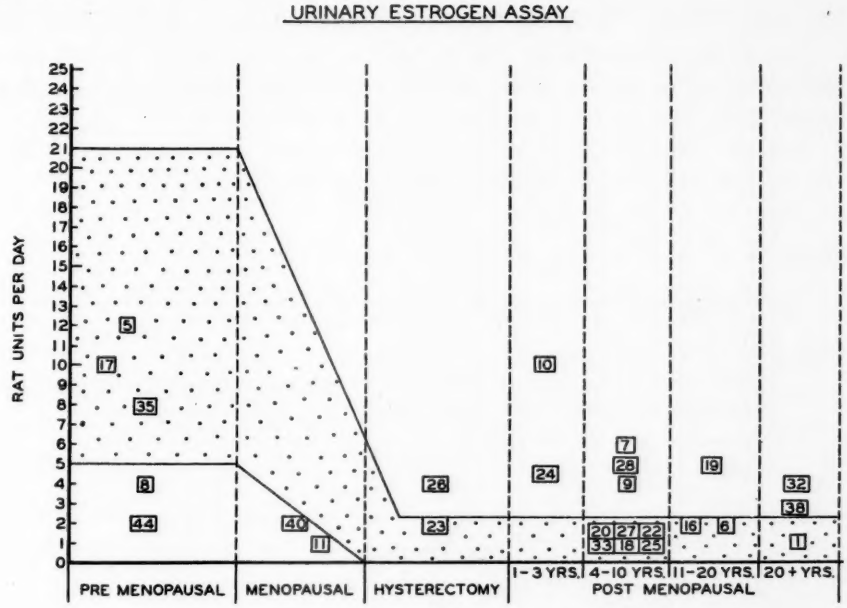

Table XI.

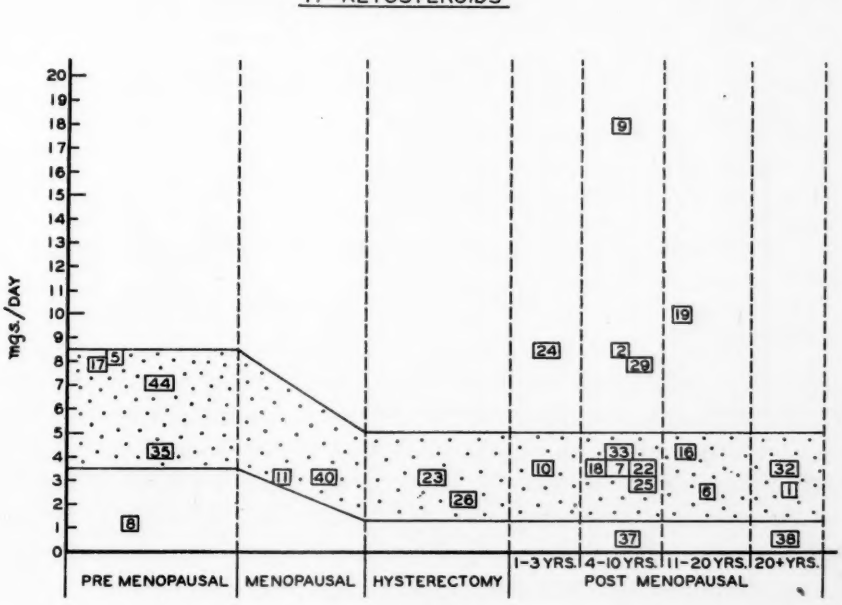

Table XII.

In order to explore further the possibility of hormonal imbalance, urinary F.S.H. determinations were carried out on 20 women in our series. The F.S.H. (gonadotropin) test is a biologic test for urinary follicle stimulating hormone, utilizing the uterine response of the immature mouse. The test as used in this study is designed to detect amounts of this hormone in excess of that present in the urine of normal premenopausal women. A positive test is the normal finding for postmenopausal women. A negative test is obtained in premenopausal women except at midcycle when a positive test may be expected. The results revealed in Table XIII show a deviation from normal in three instances (8, 44, 29), but the findings are not sufficiently unusual to be significant.

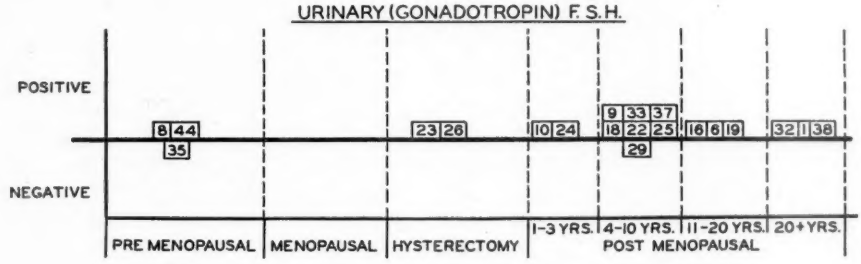

Table XIII.

Treatment: To our knowledge there is as yet no entirely satisfactory cure for leucoplakia of the vulva. Since its cause is not yet known therapy continues to be largely empirical aimed at the relief of symptoms. To this end innumerable remedies have been advocated, but none has proved entirely satisfactory. During the past year we have tried a number of different preparations, none of which has so far shown any real promise. The remedies being individually tested are:

1. Alfa-Ray ointment applied locally using airtight dressings. Five to 9 treatments at weekly intervals.
2. Ascorbic acid—1,000 mg. daily.
3. Benadryl—50 mg. three times a day orally.
4. Chlorophyll ointment applied locally.
5. Lanolin.
6. Oretone* ointment (5 mg. per c.c.) locally and oretone 10 mg. three times a day orally.
7. Pyribenzamine—50 mg. three times a day orally.
8. Petroleum jelly.

With every item listed subjective improvement has been noted by some individuals but no one remedy has been helpful for all patients. Objective improvement in the appearance of the lesion generally goes hand in hand with subjective relief. None of our 36 study group patients has yet undergone complete recovery. Vulvectomy, partial or complete, had been performed on 54 of our 143 prestudy patients. Thirteen, or 24.7 per cent, had a recurrence

*Genefously supplied by Schering Corporation, Bloomfield, N. J.

of the disease, and 9 of these are included in our present study group. We have not resorted to surgery in any of our 36 study group patients. For this there are two reasons, thus:

1. Operation has not yet been deemed necessary.

2. We do not share the optimism of many writers on the subject concerning vulvar excision since resection of the involved areas is not infrequently followed by a recurrence, and complete vulvectomy with its subsequent contraction, may result in what amounts to little less than mutilation. While this may not be important in elderly females it is a serious objection to surgical excision in young or middle-aged women. Furthermore, except for patients who develop a recurrence, once the lesion has been excised, opportunity for evaluating its clinical course and responsiveness to medical treatment ceases. Perhaps we shall resort to surgical excision in some of our study group patients in order to achieve symptomatic relief but for the time being we look upon vulvectomy as an imperfect substitute for a medical cure which we hope some day will be available.

Surgery does have a very real place, however, in the management of malignancy of the vulva and for patients with proved carcinomatous change whether on a leucoplakic basis or not, we strongly advocate radical excision including inguinal lymphadenectomy.

For his interest in humanity and generosity in making this study possible, we desire to express our thanks to W. D. Cochran.

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Discussion

DR. BENJAMIN P. WATSON.—My conception of kraurosis was that it was a condition of the vestibule and of the inner aspect of the labia minora and of the vaginal introitus itself, a sclerosing condition causing not itching but pain, which was the prominent symptom (dyspareunia), and that it went on to a very real contraction of the vulvar orifice and of the tissues around the urethrea; whereas leucoplakia was external to the vestibule, confined to the labia majora, and never invaded the vestibule itself.

It is strange that we should have this pathologic lesion which in one stage shows hypertrophy and in the next stage atrophy, and it is also rather strange that cancerous development may occur in the atrophic stage of the disease. Looking at the ordinary slides of a case of leucoplakia, one would think that carcinoma would be much more likely to develop in the hypertrophic stage where the plugs are extending down into the dermis.

There is no medical treatment so far that gives permanent relief in a true case of leucoplakia with itching and, later, cracking and fissuring, going on to carcinoma. We have tried all sorts of medicaments at the Sloane Hospital, including estrogenic ointment, stilbestrol ointment, etc., and for a time we thought we were getting results, but the improvement proved to be only temporary.

Analyzing our cases of cancer of the vulva at Sloane Hospital we found that the most common and most prolonged symptom in all cases was pruritus (80 per cent of cases had been preceded by pruritus) and that it lasted over a period of seven or eight years. If these cases of leucoplakia are followed long enough a higher percentage than that mentioned by Dr. Miller will be found to develop carcinoma.

DR. MORTIMER D. SPEISER.—It is my impression that kraurosis and leucoplakia are two separate and distinct clinical and pathologic entities which may occur singly, but are frequently combined. Kraurosis involves the vestibule and is purely an atrophic sclerosis producing a narrowing of the introitus with resulting dyspareunia. Leucoplakia, on the other hand, involves the labia majora, prepuce of the clitoris, the labia minora, as well as the perineal skin. The lesions may be symmetrical or unilateral and asymmetrical.

In so far as the histology is concerned, both entities present different pictures. The kraurosis shows an atrophy of the epidermis, while the fibrous tissue is greatly thickened. In leucoplakia, on the other hand, there are two phases, the hypertrophic, followed by the atrophic. The hypertrophic phase is associated with acanthosis and hyperkeratosis. In the connective tissue below the epithelium are evidences of edema and round cell infiltration. Elastic tissue fibers are notably absent directly below the epidermis. During the atrophic phase hyperkeratosis is still marked, but the other layers show thinning. There is a considerable collagenous deposit replacing the connective tissue directly beneath the epithelium. The elastic tissue is absent up to the layer of the subcutaneous tissue where it seems to be piled up.

The symptomatology in kraurosis is simply dyspareunia unless trauma brings about inflammation and pruritus, whereas in leucoplakia, pruritus is the outstanding symptom, and this is sometimes intractable.

The differential diagnosis of these two conditions is but one phase of the problem, since there are several other conditions which may give rise to whitish areas about the external genitals. Dr. Miller mentioned lichen planus which is characterized by the violet colored papules when it occurs elsewhere on the body, but these lesions take on a whitish appearance when present on mucosal surfaces. Thickened whitish areas known as lichenification may result from long-continued scratching. The pruritus may have its origin in a neurodermatitis, a persistent trichomonad infection, or a chronic eczematous process. Another condition giving whitish areas is lichen sclerosis et atrophicus.

DR. M. N. HYAMS.—Four and one-half years ago I saw two cases of leucoplakia vulvae; diagnosis verified by biopsy and vulvectomy done on both. Subsequently both had severe recurrence of symptoms. One was reoperated upon followed by another recurrence five months later. Then I resorted to vitamin A to combat these symptoms. Since that time eighteen patients with leucoplakia vulvae have been treated with vitamin A. In all cases thorough physical examination, biopsy specimens, and complete laboratory tests were made. Although our series is small, the results have been most encouraging. The blood picture was negative in the eighteen patients, and free hydrochloric acid was absent in 68 per cent. We had two cases of leucoplakia in Negro women. Approximately 250,000 to 500,000 Units of vitamin A were given daily by mouth supplemented by intramuscular injections of 50,000 units twice a week. In addition, all patients received fifteen minims of dilute hydrochloric acid three times daily. Marked relief of symptoms followed

this treatment in the average case. Repeated biopsy specimens showed a decided improvement in the tissues. Approximately fourteen of our patients are relieved at the present time, while the other four were total failures. Of these, two were diabetics, one was syphilitic, and the other had extensive cardiovascular disease. Apparently vitamin A therapy in the presence of severe systemic disease is useless. We hope to report our findings in the near future on 38 additional patients. We believe that with extensive vulval involvement there is a possibility of carcinoma occurring, and these cases should be operated upon. We agree that vulvectomy is not indicated in all patients with leucoplakia vulvae. Following the routine described above, the tissues take on a normal appearance, become moistened, fissures disappear, and the normal folds can again be seen. Microscopic examination showed changes of the tissues to normal. The use of vitamin A in leucoplakia vulvae, from our experience, has a definite place in its treatment.

DR. JOSHUA W. DAVIES.—I would like to mention a patient with leucoplakia who was followed for six years. This patient was bothered considerably with itching, burning and was unable to sleep. She visited various clinics; finally, after about five years, I saw her again. I was alarmed at the extensive degeneration and atrophy of the vulva. Thinking that because of the danger of malignancy she should be subjected to operation, she disappeared from our service. She turned up six months later. At that time both labia were normal and there were no fissures. I assumed that because of improved mental reaction the local area received better nutrition and that accounted for the improvement. However, she returned subsequently with her original complaints with edema, fissures, and swelling around the anus. This makes me think perhaps there is a local tissue resistance which is important in this condition.

DR. MORRIS A. GOLDBERGER.—In 1933 I reported 13 cases of kraurosis vulvae. There was much confusion at that time as to the differentiation between kraurosis and leucoplakia of the vulva. I called all my cases kraurosis vulvae. In this group there were two cases of unsuspected carcinoma. In another group of 13 cases of carcinoma of the vulva, there was coexisting kraurosis in seven.

Since then we have had 34 cases on our service at Mt. Sinai Hospital. Thirteen were diagnosed as leucoplakia vulvae on biopsy. There were five cases of leucoplakic vulvitis without kraurosis. Another 5 had both leucoplakia and kraurosis. In five cases carcinoma was found. In one of those it was grossly evident. In two cases it was unsuspected. Of these five cases, three had kraurosis and carcinoma, and two were leucoplakic with carcinoma.

Vulvectomy was done in 19 of the 34 patients with a little better than 75 per cent follow-up. The follow-up period ranged from three months to seven years.

We have gone through the period of estrogenic hormone therapy with no permanent improvement in the local condition.

We have also tried tattooing in a number of cases but the improvement was only temporary.

We have also tried large doses of vitamin B with varying results.

We are more inclined at our Hospital to divide this condition into two different categories, namely, kraurosis vulvae and leucoplakic vulvitis.

The age groups in the last thirty-four cases that we had were as follows: two were 32 years of age (menstruating women); ten were in the fourth decade of life; and the remaining twenty-two were in the fifth, sixth, and seventh decades of life.

DR. WILLIAM P. HEALY.—The gynecologist is obligated to give the patient the relief to which she is entitled, and that can be done by surgery. Recurrences can also be removed surgically.

I am very radical in my attitude toward this vulvar lesion where the patient shows evidence of damage from itching, scratching, and irritation, thickening of the tissues, hypertrophy, fissures, creases, and raw areas, because I never saw a case of epithelioma of the vulva at Memorial Hospital without a history of this supposedly nonmalignant lesion leucoplakia. There is a very long period of silence, or lack of symptoms, in cancer,

in which the cancer is actually present, but nonsymptomatic. In many cases of so-called leucoplakia or kraurosis vulvae cancer exists histologically.

The time to cure cancer of the vulva is before you know it is cancer and the patient should, therefore, be treated by vulvectomy. The coincidental lesion going down from the vulva across the perineum, then down to the perianal region also needs surgical treatment.

Many cases of perianal leucoplakia with deep creases and folds in the skin of the perianal area can be cured at the same time as the vulvectomy.

The gynecologist should certainly be able to do a vulvectomy for leucoplakia of the vulva or kraurosis vulvae and retain normal function.

DR. FRANK R. SMITH.—The incidence at the Memorial Hospital of cancer of the vulva in Negro women preceded by leucoplakia is about the same as the cross-section of the clinic.

The low incidence of arteriosclerotic women with cancer of the vulva is surprising.

Because of the probability of subsequent carcinoma, the treatment is surgical. Forty per cent of patients coming to Memorial Hospital with cancer of the vulva had prior medical therapy for leucoplakia and pruritus—injections, estrogenic applications, etc.

Women who suffer from pruritus are ripe subjects for psychoneurosis unless given relief, and therefore the factor of psychoneurosis may be effect rather than cause.

DR. HOWARD C. TAYLOR, JR.—We have theorized a lot about constitutional causes for leucoplakia of the vulva, but we must remember that there is also the matter of local tissue predisposition. The disease occurs in circumscribed areas, characteristically on the inner sides of the labia.

Now it may occur here for one of two reasons, either because of a congenital intrinsic peculiarity of the vulval skin, or else because of the geographical position of the skin which brings surfaces in contact in that area.

The second possibility is proved by the fact that when you do a complete vulvectomy and bring in nonspecific skin to the introitus of the vagina you later get development of leucoplakia fairly frequently in the nongenital skin which you have brought in to the vulval region. From this often repeated cervical experiment it appears that the local factor is to be found in the superficial geographical conditions incidental to the apposition of the two layers of skin at the introitus of the vagina and not to any congenital peculiarity of skin associated with the genital tract.

DR. MILLER (Closing).—This report represents an attempt to evaluate some of the theories, and there have been a great many of them, concerning the cause of leucoplakia. It is also an attempt to learn something about the clinical course of leucoplakia. We have taken some of the theories and analyzed them and presented certain data bearing on these theoretical causes, but of course much work remains to be done.

STUDIES ON THE HUMAN CORPUS LUTEUM*†

Histologic Variations in Corpora Lutea and in Corpus Luteum. Endometrial Relationships at the Onset of Normal Menstruation

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IT IS rather generally accepted that the life cycle of the human corpus luteum, the cycle of the endometrium, and the relationships of these two tissues one to another are constant and are not subject to variations. During their active normal functioning state we believe that this is usually true. Variability does occur, however, in these two tissues and in their relationships during the regressive stage, principally near and just after the onset of menstruation each month.

It is the purpose of this presentation to demonstrate the normal variations and to discuss their clinical importance. Endometrial studies are frequently made in an effort first to determine the presence or absence of a corpus luteum, second, to estimate the functional capacity of the corpus luteum in preparing the endometrium for pregnancy, and third, to study corpus luteum activity in relation to abnormalities of the menstrual cycle. Without proper evaluation of the normal variations these clinical studies may be subject to misinterpretation.

Material

The tissues for this study consist of the uterus with the endometrium and the corpus luteum in each instance. The specimens were obtained from patients who had completely normal menstrual cycles. The ages of the patients varied from 23 to 47 years. Seven of the patients had fibroids and/or residues of pelvic infection. One of the patients had uterine prolapse of a normal uterus, one had a retrodisplaced normal uterus, and one had a normal uterus. Although pathologic lesions were present there had been no alteration of the menstrual cycles from the normal. The menstrual histories were carefully checked during the patient's hospital stay.

The tissues were obtained as surgical specimens. These were studied grossly and then placed in various fixing solutions within five minutes after the blood supply was clamped. The multiple blocks of endometrium were chosen from regions where the endometrium did not overlie a fibroid. This was done to avoid mechanical distortion of the tissue.

Three specimens obtained prior to the onset of menstruation were selected as representative of this period. Seven specimens removed from patients on day 1 of menstruation are reported.

SPECIMEN 255.—Day 27 of cycle, aged 35 years, para vi, gravida vi; menstrual history: Onset at 14 years of age, 26- to 35-day cycles, five days' flow.

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†Aided by the C. V. Essroger Research Fund and a grant from the Billings Medical Club, Chicago.

Pathologic diagnosis: Normal uterus.

Corpus luteum: The dimensions before fixation were 1.2 by 0.8 by 0.8 cm. The wall was thin. The granulosa lutein cells in many regions stained well, had intact, well-stained nuclei, and resembled functioning cells (Fig. 1). There were some shrunken cells with pyknotic nuclei scattered throughout the layer. In one local region cell degeneration was markedly advanced. (Fig. 5, Am. J. Obst. & Gynec. **44**: 6, 1942.) The ingrowth of connective tissue was considerable. The central border was composed of a thick layer of well-organized connective tissue. In the granulosa lutein layer the vessels were collapsed and contained no blood. The theca lutein cells were abundantly distributed about the entire periphery and their nuclei were intact.

Endometrium: The endometrium was as thick as 0.45 cm. prior to fixation. The glands were secretory in character, were squashed, and the lumens contained secretion. Involution had occurred. (Fig. 6, Am. J. Obst. & Gynec. **44**: 6, 1942.) There were a few scattered lymphocytes superficially. There was no extravasation of blood. The spiral arteries reached to the surface epithelium.

Specimen 149.—Day 30 of cycle, aged 36 years, para ii, gravida ii. Menstrual history: Onset at age 16 years, 28-day cycle, three to four days' flow.

Pathologic Diagnosis: Uterine prolapse.

Corpus luteum: The dimensions before fixation were 2.5 by 2.0 by 1.2 cm. The wall was thin and wavy. The granulosa lutein cells were shrunken, vacuolated, and in many the nuclei were pyknotic. (Fig. 7, Am. J. Obst. & Gynec. **44**: 7, 1942.) The cells in all regions of the granulosa lutein layer had a similar degree of degeneration. The ingrowth of connective tissue was marked. The central border was composed of a dense layer of connective tissue. The vessels were collapsed, contained no blood, and were surrounded by a thick layer of connective tissue. The theca lutein cells were sparse and were located principally in the angles of the folds of the granulosa lutein layer.

Endometrium: The endometrium was as thick as 0.5 cm. prior to fixation. The squashed glands showed characteristic secretory activity. Involution had occurred. There was an infiltration of leucocytes and lymphocytes superficially. (Fig. 8, Am. J. Obst. & Gynec. **44**: 7, 1942.) There was some extravasation of blood just beneath the surface epithelium. In this region some of the cells of the surface epithelium had pyknotic nuclei. The spiral arteries reached to the surface.

Specimen 221.—Day 28 of cycle, aged 34 years, para ii, gravida ii. Menstrual history: Onset at age 13 years, 28-day cycle, 5 days' flow.

Pathologic diagnosis: Small myoma and residues of pelvic infection.

Corpus luteum: The dimensions before fixation were 2.5 by 1.5 by 1 cm. The granulosa lutein layer is arranged in the usual folds, and some portions are thinner than others. In some regions the granulosa lutein cells are shrunken, in others there are frequent cells with pyknotic nuclei, and in others the cells are large, even, and show little evidence of regression. The central border consists of a thick dense layer of connective tissue. The blood vessels in the granulosa lutein layer are straight, narrow, and contain no blood cells. About the vessels the connective tissue is abundant.

The theca cells are arranged in the angles of the folds, have round plump nuclei and vacuolated cytoplasm.

Endometrium: The endometrium in the fixed and stained preparation is 4 mm. thick. The glands are typically secretory. Involution has occurred. There is marked infiltration of leucocytes and lymphocytes and a moderate extravasation of red blood cells superficially. There are occasional local collections of red blood cells immediately beneath the surface epithelium. A

characteristic loosening up of the stromal cells in the superficial zone has occurred. The spiral arteries reach to the surface.

SPECIMEN 325.—Day 1 of cycle. Patient began to menstruate three hours prior to operation. Age 29 years, para i, gravida i. Menstrual history: Onset at 12 years of age, 24-day cycle, five days' flow.

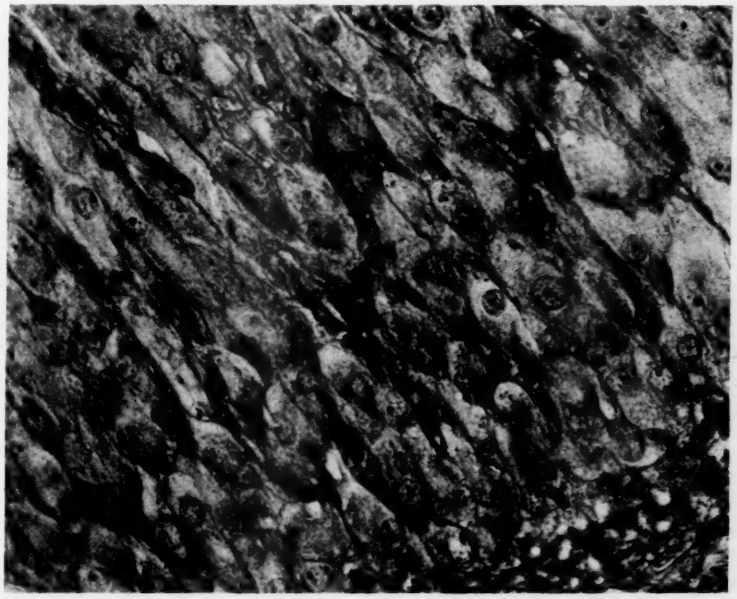

Fig. 1.—Specimen 255. In this portion of the corpus luteum the granulosa lutein cells stain well, are intact, and resemble functioning cells. (Photomicrographs of degenerating cell regions and the endometrium of this specimen are shown in Figs. 5 and 6, Am. J. Obst. & Gynec. Vol. 44: 6, 1942.)

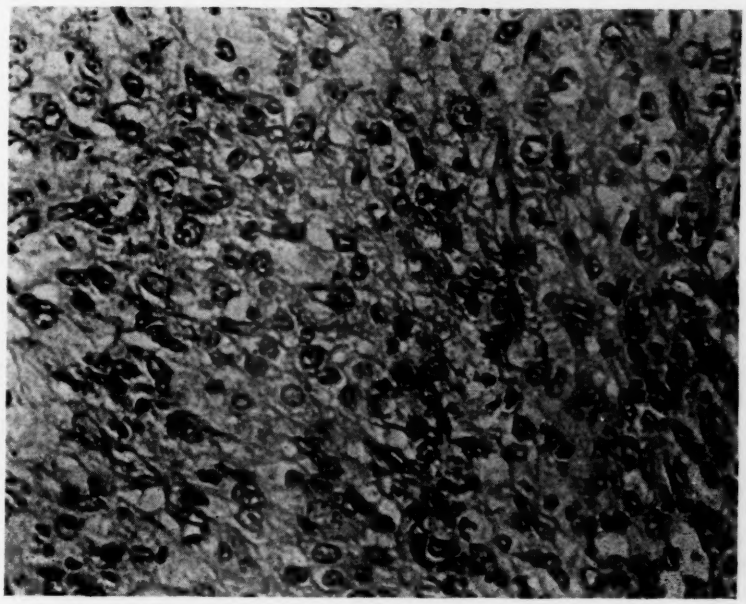

Fig. 2.—The granulosa lutein cells are uniformly involved in an advanced degree of degeneration. (Speciment 325; first day of menstruation.)

Pathologic diagnosis: Small uterine myomas.

Corpus luteum: The dimensions before fixation were 2 by 0.9 by 0.8 cm. The granulosa lutein cells throughout the entire corpus luteum were uniformly degenerated (Fig. 2). The cells were small, irregular in shape, had clear cytoplasm and pyknotic nuclei. In no region were there intact granulosa lutein cells. There was an abundant ingrowth of connective tissue throughout this layer, but the connective tissue border along the central cavity was scant, was not organized, and was consistent with that of a much younger corpus luteum. The blood vessels were narrow, empty, and were surrounded by considerable connective tissue.

The theca interna cells were smaller than the granulosa lutein cells, had vacuolated cytoplasm, and many had irregular, pyknotic nuclei.

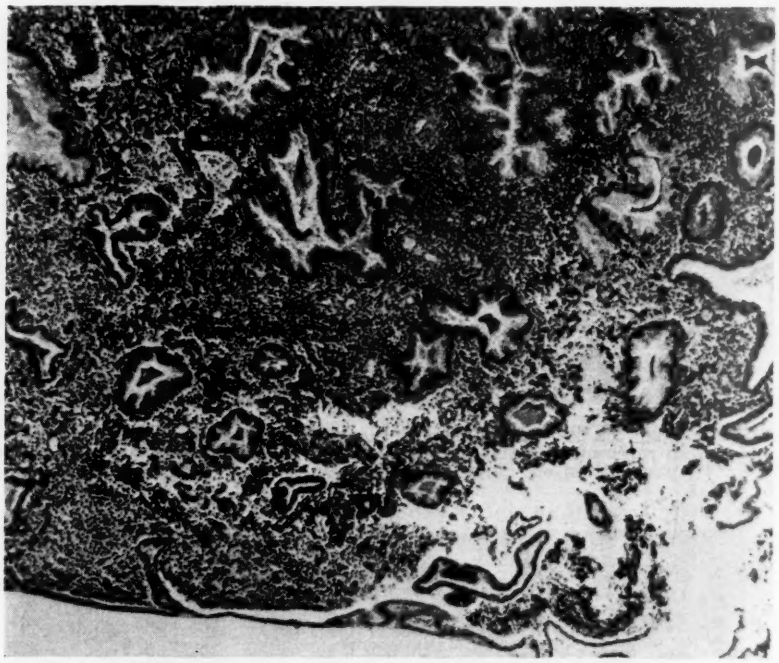

Fig. 3.—The endometrium of Specimen 325 has local regions of desquamation. Previous secretory activity of the gland cells is indicated by the abundant secretion in the gland lumens. The corpus luteum of this specimen is shown in Fig. 2.

Endometrium: The endometrium in the fixed and stained preparation was as thick as 0.5 cm. The glands were secretory in type. The spiral arteries reached to the surface. Involution had occurred. Throughout the superficial zone there was an extensive infiltration of leucocytes and lymphocytes, extravasation of red blood cells, and a loosening up of the stromal cells. Subepithelial hematomas were frequent. In places the surface epithelium was detached from the underlying stroma. In several small microscopic regions there was desquamation of the superficial endometrium (Fig. 3).

SPECIMEN 303.—Day 1 of cycle. Began to menstruate eighteen hours prior to operation. Age 23 years, para i, gravida i. Menstrual history: Onset at 12 years of age, 28-day cycle, two to seven days' flow.

Pathologic diagnosis: Residues of pelvic infection.

Corpus luteum: The diameter prior to fixation was 2.0 cm. The granulosa lutein cells have little evidence of degeneration (Fig. 4). Many of the cells are still large and the nuclei are round or oval and stain well. Shrinkage in

Fig. 4.—The granulosa lutein cells shown in this photomicrograph of Specimen 303 (first day of menstruation) are typical of all cells throughout the granulosa lutein layer. The cells are intact, are only slightly reduced in size, and have little evidence of degeneration. Some blood is still present in the vessels in the granulosa lutein layer.

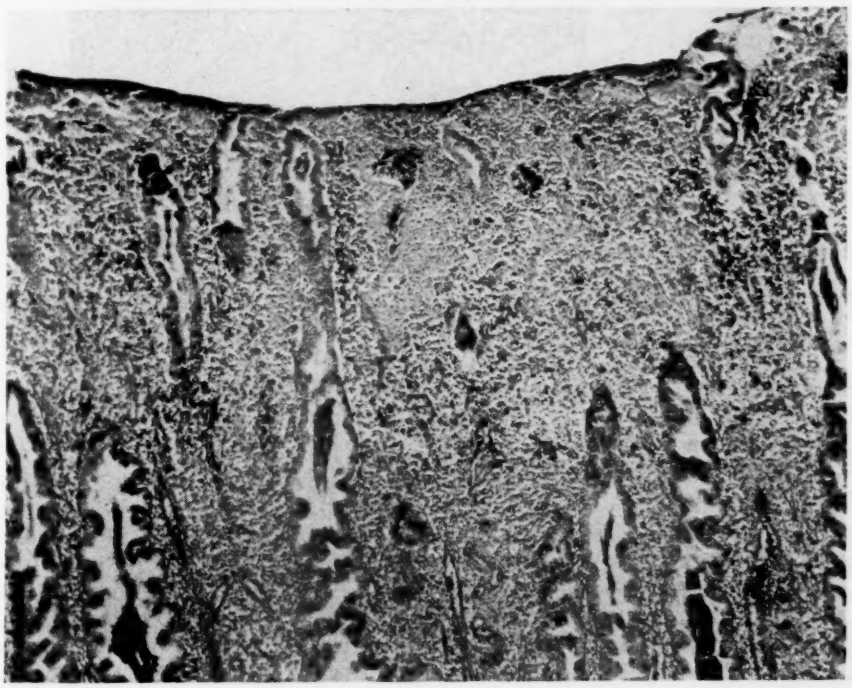

Fig. 5.—The findings in the endometrium indicate impending menstruation and in some small regions desquamation has occurred. Histologic evidence of some continued corpus luteum secretory activity is shown. (Specimen 303.)

some cells has occurred but it is not great. There is little vacuolization of these cells and only a few cells have pyknotic nuclei. Some of the blood vessels in this layer still contain red blood cells. Most, however, are empty. The vessels have rather thick connective tissue borders. The ingrowth of connective tissue is abundant, and the border about the central cavity is thick and well organized.

The theca interna cells are abundant. There is no evidence of pyknosis.

Endometrium: The endometrium in the fixed and stained preparation is 0.3 cm. thick. The secretory glands are squashed and the edema has disappeared from the stroma. The spiral arteries reach to the surface. Involution has occurred. Throughout the superficial zone there is an extensive infiltration of leucocytes and lymphocytes, extravasation of red blood cells, and a loosening of the stromal cells (Fig. 5). In some regions desquamation has occurred but loss of tissue is scant.

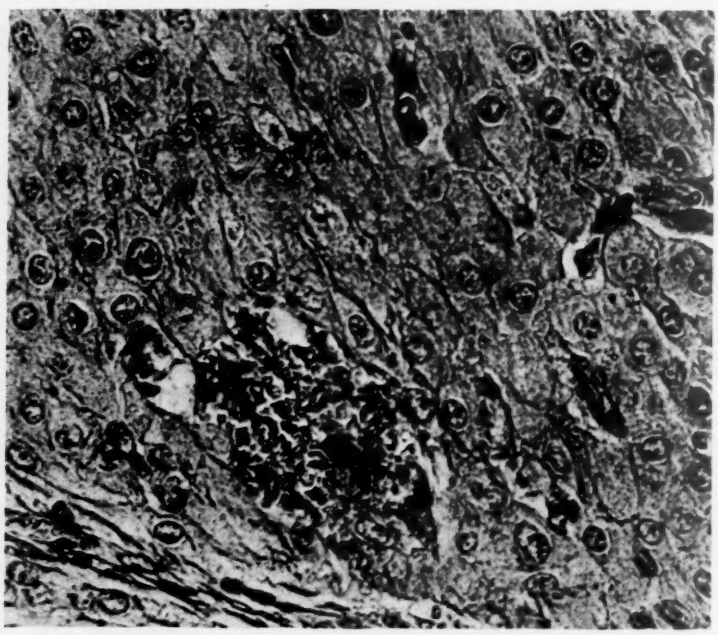

Fig. 6.—The granulosa lutein cells throughout the entire layer evidence slight regression only by a slight reduction in cell size. The cell shapes, staining qualities, and nuclei are similar to those of the physiologic active gland cells. (Specimen 106; first day of menstruation.)

SPECIMEN 106.—Day 1 of cycle. Began to menstruate one hour prior to operation. Age 41, para iii, gravida iii. Menstrual history: Onset at age 11 years, 28-day cycle, seven to eight days' flow.

Pathologic diagnosis: Uterine myoma and residues of pelvic infection.

Corpus luteum: The diameter before fixation was 1.5 cm. The granulosa lutein cells were intact and resembled functioning cells (Fig. 6). Some still remained large, but most were reduced in size. Occasional nuclei were pyknotic. Most, however, stained well and were round or oval. Degenerative changes were minimal. The cytoplasm stained evenly. The blood vessels throughout the granulosa lutein layer were narrow and collapsed. Some contained red blood cells. The ingrowth of connective tissue was moderate. The central cavity had a well-organized connective tissue border.

The theca interna cells were numerous, were smaller than the granulosa lutein cells, had vacuolated cytoplasm, and some of the nuclei stained poorly and had irregular shapes.

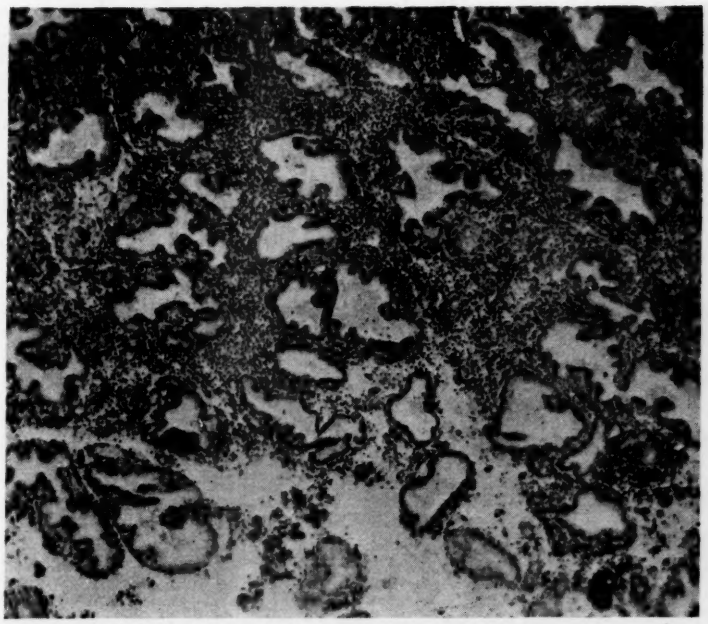

Fig. 7.—The endometrium (Specimen 106) has undergone more desquamation than usual for a specimen removed within one hour after the onset of menstruation. The evidence of antecedent stimulation is less than that in Specimen 303, Fig. 5. The corpus luteum is shown in Fig. 6.

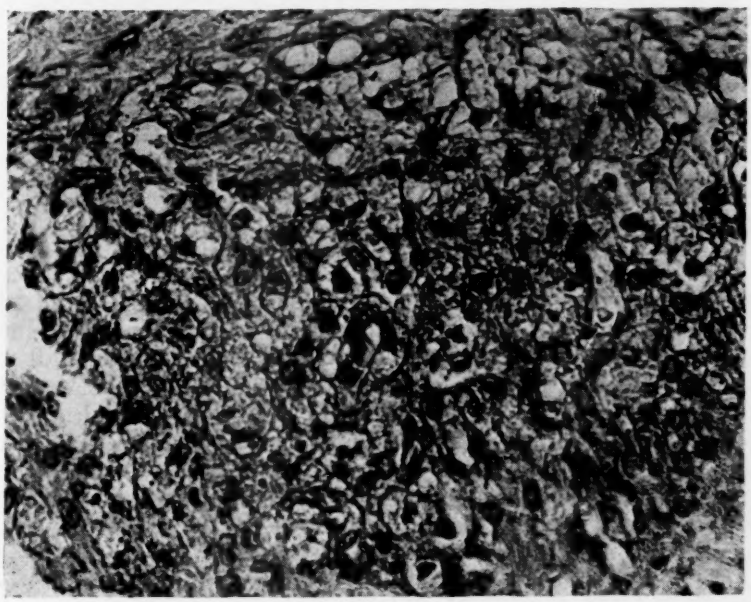

Fig. 8.—This photomicrograph of a portion of the corpus luteum (Specimen 224; first day of menstruation) shows the granulosa lutein cells in an advanced degree of degeneration which is similar to Specimen 325, Fig. 2.

Endometrium: The endometrium in the fixed and stained preparation varied from 0.2 to 0.5 cm. in thickness. Desquamation of the endometrium was extensive (Fig. 7). In no sections was the surface epithelium present. Glands and spiral arteries jutted above the very irregular surface. The glands had evidence of antecedent secretory activity as determined by secretion in the lumens. The cells themselves in some glands had no evidence of secretory activity.

SPECIMEN 224.—Day 1 of cycle. Began to menstruate two hours prior to operation. Age 37 years, para i, gravida i. Menstrual history: Onset at the age of 14 years, 28-day cycle, three to five days' flow.

Pathologic diagnosis: Uterine myomas.

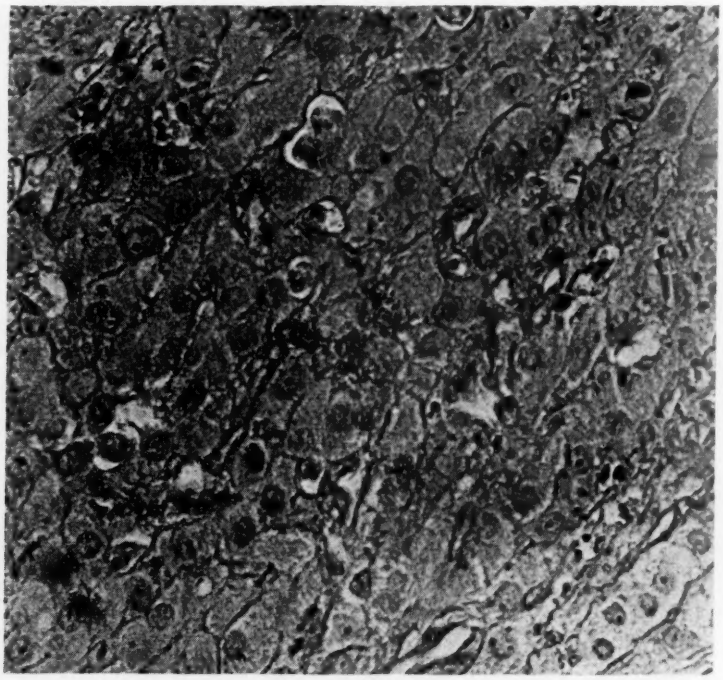

Fig. 9.—In other regions of the corpus luteum shown in Fig. 8, the granulosa lutein cells remain intact and evidence regression only by reduction in cell size.

Corpus luteum: The dimensions of the corpus luteum before fixation were 1.0 by 0.8 by 0.5 cm. Throughout most regions of the granulosa lutein layer the cells were shrunken and vacuolated (Fig. 8). Some had small nuclei and in many the nuclei were pyknotic. In other regions the cells were large, the cytoplasm stained evenly, the nuclei were large, round or oval, and there was little evidence of degeneration (Fig. 9). There was marked infolding of the entire layer. The blood vessels in the layer were narrow, straight, collapsed, and contained no blood. There was a moderate ingrowth of connective tissue. The connective tissue border about the central cavity was not very dense or thick. The centrum contained a large amount of blood.

The theca interna cells were smaller than the granulosa lutein cells, were highly vacuolated, and many had pyknotic nuclei.

Endometrium: The thickest portion of the endometrium in the fixed and stained preparation was 0.25 cm. The endometrial surface was irregular, and considerable desquamation of tissue had occurred (Fig. 10). The glands evidence still some slight secretory activity in some regions, while in others the

glands were not secretory in character, but their lumens contained secretion as evidence of their antecedent activity.

SPECIMEN 66.—Day 1 of cycle. Began to menstruate one hour before operation. Age 24 years, para i, gravida i. Menstrual history: Onset at the age of 13 years, 28-day cycle, four to five days' flow.

Pathologic diagnosis: Normal uterus.

Corpus luteum: The dimensions before fixation were 1.8 by 1.2 by 1.0 cm. Degenerative changes involve the granulosa lutein cells rather uniformly throughout the granulosa lutein layer. The cells were shrunken, irregular in size and shape, vacuolated, and many contained pyknotic nuclei. The blood vessels throughout the layer were narrow and contained no blood. The ingrowth of connective tissue was marked. Along the central cavity the thick connective tissue border was well organized. There was some blood in the central cavity.

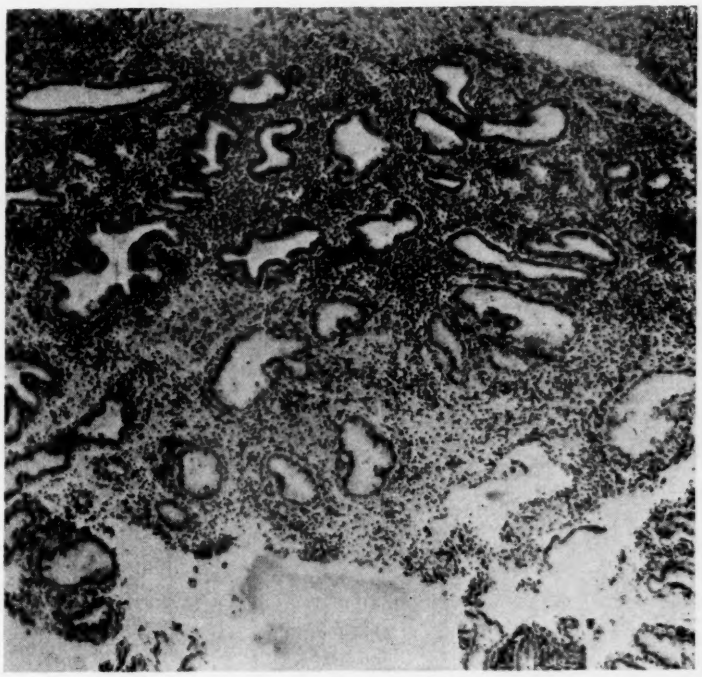

Fig. 10.—The endometrium (Specimen 224) has undergone extensive desquamation. There is considerably less evidence of antecedent secretory activity than in Specimen 325, Fig. 3. The corpus luteum of this specimen is shown in Fig. 8 and Fig. 9.

The theca cells showed the usual grouping and vacuolization. Pyknosis was rare.

Endometrium: Before fixation the thickness of the endometrium varied from 0.2 to 0.4 cm. The surface of the endometrium was irregular and ragged. The loss of tissue was considerable. Many of the glands retained little evidence of secretory activity.

SPECIMEN 215.—Day 1 of cycle. Began to menstruate eighteen to twenty-four hours prior to operation. Age 41 years, para iv, gravida ix. Menstrual history: Onset at 13 years, 26-28-day cycle, five days' flow.

Pathologic diagnosis: Uterine myomas.

Corpus luteum: The dimensions before fixation were 1.5 by 1.2 by 0.8 cm. There was a marked folding of the wall. By far the greater number of the

granulosa lutein cells were only reduced in size and had moderate vacuolization. The nuclei and nucleoli remained intact and appeared normal. Pyknosis was not prominent. In some small local regions the granulosa lutein cells had degenerated more and had nuclear pyknosis, irregular sizes and shapes, and clear cytoplasm. The connective tissue was abundant and had extended through the layer, and was organized as a thick border around the central cavity. The central cavity contained a small amount of blood.

The theca cells were small, vacuolated, and had round intact nuclei.

Endometrium: The greatest thickness was 0.2 cm. The surface was irregular, and the surface epithelium was lost in all but a few regions. Desquamation, while general throughout the endometrium, was only moderate, since the regions still covered with epithelium were approximately as thick as those undergoing slough. Some of the glands showed slight to moderate secretory characteristics. In some regions the glands were straight, and demonstrated little antecedent secretory activity.

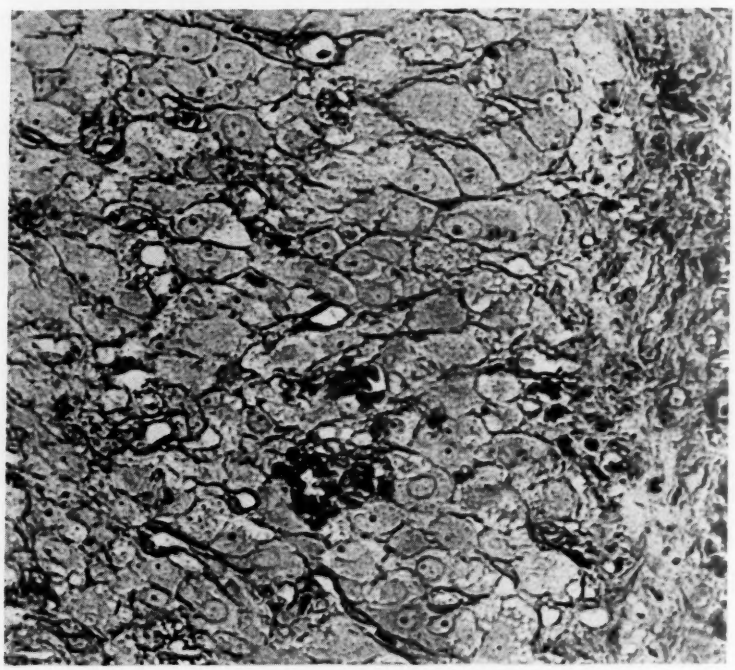

Fig. 11.—Many of the granulosa lutein cells (Specimen 13; first day of menstruation) have evidence of degeneration. Many are only reduced in size and some remain large, stain well, and have round large well-stained nuclei.

SPECIMEN 13.—Day 1 of cycle. Began to menstruate three hours prior to operation. Age 47 years, para iii, gravida viii. Menstrual history: Onset at 14 years of age, 28-day cycle, six to seven days' flow.

Pathologic diagnosis: Uterine myoma.

Corpus luteum: The stigma point was readily identified. The granulosa lutein layer (Fig. 11) was thin and only moderately wavy. The cells were, for the most part small, irregular in shape, many were vacuolated, and pyknosis was common. In some regions, however, the cells were plump, had even stained cytoplasm and normal round or oval nuclei. The blood vessels were narrow and a few contained some blood. There was a moderate ingrowth of connective tissue. The connective tissue border about the central cavity was thick and well organized. There was a slight amount of blood in the central cavity.

The theca cells had the usual vacuolization, and some had pyknotic nuclei.

Endometrium: The thickest portion of the endometrium after fixation and staining was 0.15 cm. While slough had occurred, the surface of the endometrium was more even than in the other menstruating specimens. No portion of the endometrium was covered with epithelium. The stroma was dense. The glands showed no evidence of present or previous secretory activity (Fig. 12). The gland cells were characteristic of those stimulated only by estrogens.

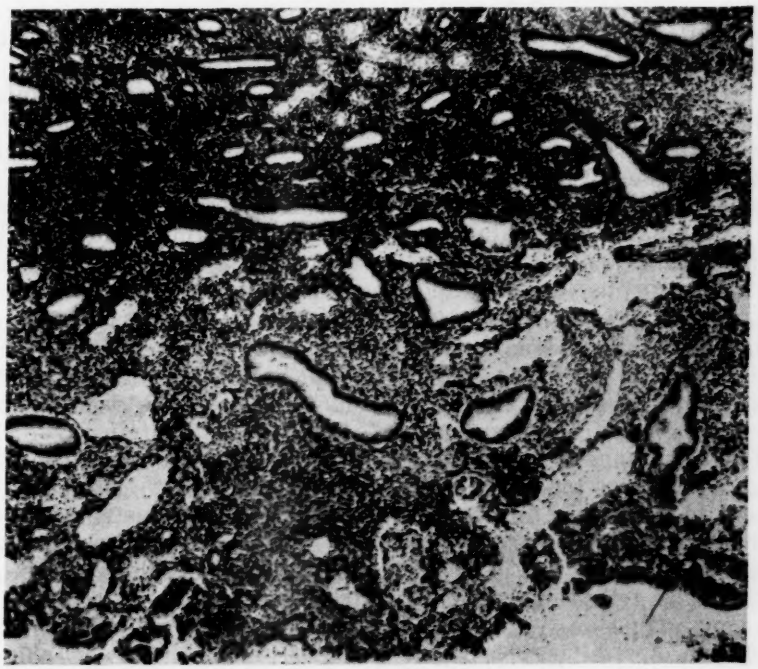

Fig. 12.—The endometrium (Specimen 13) has undergone desquamation in all portions. There is no evidence of antecedent secretory stimulation of the glands. This endometrium is typical of that described as anovulatory menstruation but in this instance a corpus luteum was present (Fig. 11).

Histologic Variations in Granulosa Lutein Cells Immediately Prior to and During Day 1 of Menstruation

In the human corpus luteum, degeneration of the granulosa lutein cells is first noted four to six days before the onset of menstruation (Brewer, 1942). This degeneration is a slow and gradual process, and in its early phases can be a reversible reaction if pregnancy ensues. It is not a process that occurs suddenly at the onset of menstruation, and it does not typically involve all the cells of the granulosa lutein layer uniformly. In the rhesus monkey, Corner (1936 and 1945) concluded that degeneration of the corpus luteum begins at the onset of menstruation, and that the resultant breakdown of cells occurs uniformly throughout. In the corpus luteum of the swine, he (1915) described an early onset of regression and observed that the cells were involved in an irregular way. There may be differences in the degenerative process in various animals.

Histologic variations occur in the degenerative phase of the granulosa lutein cells of the human being. The degenerative process may uniformly involve all of the cells throughout the granulosa lutein layer in some human corpora lutea as described for the monkey and is exemplified by Specimens 325 (Fig. 2) and 66. In Specimen 325, obtained within three hours after the onset of menstruation (as timed by the appearance of gross blood), the picture

of degeneration of the granulosa lutein cells was identical to that described by Corner (1945) in day 1 monkey corpora lutea. In this specimen the meager amount of connective tissue extending into the central cavity and the lack of its typical organization as a dense border about the central cavity was unusual in human day 1 corpora lutea, and its significance was not immediately apparent. It resembled more closely the findings in earlier stages of life of the corpus luteum. Specimen 66, removed one hour after the onset of gross bleeding, also showed degeneration of the cells rather uniformly throughout the granulosa lutein layer. The degree of degeneration, however, was considerably less than in Specimen 325. In these two corpora lutea, removed soon after the onset of gross bleeding, there was a distinct variability in the degree of cellular degeneration, although the changes involved all of the cells. A similar picture was seen in some corpora lutea prior to the onset of menstruation. Specimen 149 removed on day 30 of the cycle, prior to the onset of menstruation, showed a marked degeneration throughout. The cells were shrunken, vacuolated, irregular, and many had pyknotic nuclei. The endometrial findings indicated that menstruation will begin shortly. Photomicrographs of this corpus luteum and the associated endometrium are shown in Figs. 7 and 8, Am J. Obst. & Gynec. **44**: 7, 1942.

In some instances degeneration involves only local groups of cells rather than all the cells of the layer. Such is noted before the onset of menstruation (Specimen 255, Fig. 6, Am. J. Obst. & Gynec. **44**: 6, 1942, and Specimen 221). Some of the cells in other portions of the granulosa lutein layer of corpora lutea showed evidence of regression only by reduction in cell size. Numerous other cells showed no evidence of degeneration (Fig. 1). These findings were also present in specimens obtained on the first day of menstruation. In Specimens 224 and 215 there were many intact granulosa lutein cells, even though menstruation had begun (Fig. 9). There was considerable variability in the numbers of such cells remaining in various specimens. A localized region of degeneration in Specimen 255 is shown in Fig. 5, and the associated endometrium in Fig. 6, Am. J. Obst. & Gynec. **44**: 6, 1942.

In Specimen 13 removed on the first day of menstruation, most cells were reduced in size throughout, and many were in a more advanced state of necrosis. Some cells, however, remained intact, were large, stained well, and had well-stained round nuclei (Fig. 11). The variations in these three corpora lutea removed on day 1 of menstruation were apparent, and the difference between these and the two day 1 cases (Specimen 325, Fig. 2, and Specimen 66) was striking. The finding of granulosa lutein cells with little evidence of degeneration in some portions of the corpus luteum was not unusual in specimens obtained on the first day of normal menstruation.

In some corpora lutea almost all the granulosa lutein cells may remain intact after the onset of menstruation (Specimen 303, Fig. 4, and Specimen 106, Fig. 6). Many of the cells may be reduced in size but staining qualities, shapes, and intact nuclei are retained. Cellular degeneration is minimal. This observation is in distinct contrast to the findings in the rhesus monkey (Corner, 1936 and 1945), and to that found in some day 1 cases, such as Specimens 325, Fig. 2, and 224, Figs. 8 and 9.

It is apparent that there is considerable histologic variation in the granulosa lutein cells during the phase of degeneration of the corpus luteum just prior to and immediately after the onset of menstruation. The variability is noted in the different corpora lutea of this stage and also in the same corpus luteum. The differences that occur between some corpora lutea are shown in Specimen 325 (Fig. 2) as contrasted with Specimens 303 (Fig. 4) and 106 (Fig. 6). Variations occurring in the same corpus luteum are shown in Specimen 224 (Figs. 8 and 9).

Variations in the Endometrial Corpus Luteum Relationships Prior to and During Day 1 of Menstruation

The endometrium of Specimen 255 (day 27) had involuted and there was some infiltration of lymphocytes and leucocytes in the superficial portion. (Fig. 6, Am. J. Obst. & Gynec. **44**: 6, 1942.) The endometrium of Specimen 221 (day 28) was nearer to the time of onset of menstruation as indicated by the more extensive infiltration of lymphocytes, extravasation of blood, and the presence of small subepithelial hematomas. The granulosa lutein cells of the corpus luteum of Specimen 221, however, showed approximately the same histologic evidence of degeneration as Specimen 255.

The endometrium of Specimen 149 (Fig. 7, Am. J. Obst. & Gynec. **44**: 7, 1942) showed less histologic evidence of impending menstruation than Specimen 221, but showed more than Specimen 255. The degree of degeneration of the granulosa lutein cells in Specimen 149 was considerably greater than in Specimen 255 and 221.

These specimens indicate that there are histologic variations in the corpus luteum-endometrial relationships just before the onset of menstruation.

During the first day of menstruation the endometrial findings may vary considerably in the degree of secretory activity as well as in the stage of the menstrual desquamation. Bartelmez (1931) has described such variations, and also has adequately demonstrated the variability in different portions of the same uterus.

In the group of seven first day cases studied, the endometrium in three showed scant slough of tissue. (Specimens 325, 303, and 13.) The endometrial findings in Specimen 325 (Fig. 3) and 303 (Fig. 5) were quite comparable, showing about the same amount of desquamation and comparable degrees of antecedent secretory activity. Specimen 325 was obtained within three hours after the onset of menstruation, while the patient from whom Specimen 303 was obtained had been spotting blood for 18 to 24 hours prior to operation. The granulosa lutein cells of Specimen 325 were uniformly involved in a marked degree of degeneration (Fig. 2). These cells in Specimen 303, however, remained intact and showed little or no evidence of degeneration (Fig. 4). The variability in the endometrial-corpus luteum relationship in these two specimens is apparent.

The moderate desquamation was considerably more and the endometrial gland secretory activity was less in Specimen 215 than in 325, yet the degree of degeneration evident in the granulosa lutein cells of 215 was much less than in 325. Here again the histologic findings indicate a variation in day 1 endometriums as well as in the corpus luteum-endometrial relationship.

Extensive endometrial slough was noted in three day 1 specimens (224, Fig. 10; 66; 106, Fig. 7). The degree was more than anticipated in specimens obtained within one to three hours after the onset of menstruation. The degree of desquamation was much greater than in other day 1 cases studied here. The evidence of glandular secretion was approximately the same in these three specimens. The three corpora lutea associated with these three endometrial specimens differed greatly from one another histologically. One (Specimen 66) had considerable cellular degeneration uniformly throughout the granulosa lutein layer. One (Specimen 224) showed only local regions of degeneration in this layer while other regions contained intact cells. One (Specimen 106) showed little or no degeneration of the granulosa lutein cells. Thus, the endometriums of these three were histologically similar but the corpora lutea were quite different.

In Specimen 13 the endometrium was thin, showed no evidence of preceding progesterone stimulation, and was typical of that described as anovulatory

menstruation (Fig. 12). It was not an instance of anovulatory menstruation, for a corpus luteum was present in the ovary. The degenerating granulosa lutein cells were uniformly involved as in Specimens 325 and 66, but the degree of degeneration was markedly less. There was considerable variation between this endometrium and the endometriums of the other normal day 1 specimens. This specimen varies considerably from that accepted as a normal standard. A definite explanation of this relationship cannot be made on the basis of histology alone. Several possibilities exist. It is possible that the endometrium had been stimulated and that the signs of antecedent secretory activity had disappeared. It is possible that the corpus luteum, while histologically normal and consistent in appearance with corpora lutea of the same stage, was, from a functional standpoint, unable to stimulate the endometrium. It is also possible that the ovarian stimulation was present in adequate amounts, but the endometrium, as an end organ, was unable to respond to normal stimulation. Irrespective of this, three definite statements can be made. One, ovulation had occurred as proved by identification of the rupture point and the fact that a corpus luteum had formed. Two, from a histologic standpoint the corpus luteum was normal for this stage of the cycle. Three, the endometrium was similar to that described as typical of anovulatory menstruation. This specimen well demonstrates the possible error in making a positive statement that ovulation had or had not occurred from a study of the endometrium alone.

The variations in the different endometriums and the variations that occur in different regions of the same endometrium just prior to and during the first day of normal menstruation are more considerable than is generally recognized. Bartelmez (1931) described and stressed these endometrial variations in the same and different uteri. In one 28-day case he found that the gland cells contained little glycogen and that the cells lacked secretory evidence. Since there was secretion in the gland lumen indicating antecedent activity, he concluded that the stimulus to secretion had ceased before menstruation into the lumen had begun. In an endometrium obtained eight hours after the onset of bleeding, the glands similarly lacked secretory evidence. He also described two other similar first day cases. In three day 1 cases he found evidence in the endometrium of continued corpus luteum activity after menstruation had begun. Our findings reported here are quite comparable.

A review of the findings in the corpora lutea obtained just before or on day 1 of menstruation indicates that there are variations between the different corpora lutea and also between different regions of the granulosa lutein layer of a single corpus luteum. There are variations in secretory activity and in extent of desquamation in the endometriums as well during this period. Not only do these tissues vary among themselves but there is so much variation that an absolute constant pattern cannot be established. A study of the endometrium during this period in the cycle does not accurately reflect the histological picture of the corpus luteum. Similarly, a histologic study of the corpus luteum does not reflect the true state of the endometrium. (Specimens 303, 106, and 13.) It is possible that during this phase of degeneration the histology of the granulosa lutein cells may not reflect a true index of the degree of functional activity of the corpus luteum.

The observations reported here have clinical as well as academic interest. Endometrial biopsies are being more and more frequently studied in endocrine and sterility problems. In the numerous reports the presence or absence of corpora lutea and the qualitative and quantitative functional capacities of the structures are estimated from the histology of the endometrium. On this basis clinical diagnoses are made and treatments instituted. In order that errors are avoided, it is necessary that the histologic variations in the relationship between the corpus luteum and endometrium be evaluated. This is particu-

larly true since it is rather universally advocated that endometrial biopsies should be taken on day 1 of menstruation and it is at this time that the variations are the greatest.

Endometrial biopsies obtained on day 1 of menstruation do not give accurate interpretations of previous endometrial responses to stimulation. The endometrial tissues are ischemic, partially necrosed or in some regions necrotic, and may be partially or completely inactive from a functional standpoint. In many instances the tissues in some regions reflect antecedent stimulation and activity, while in others such signs of stimulation and activity are greatly diminished or completely wanting. These marked changes have been noted here as soon as one hour after the onset of menstruation. Bartelmez (1931) found them prior to the onset of menstruation.

The endometrium obtained on day 1 of menstruation likewise does not give accurate interpretation of previous corpus luteum secretory activity. It reflects only the diminution or complete cessation of functional activity of that gland which is degenerating or has degenerated. This it does none too accurately as has been shown.

Accurate interpretation of functional activity can be obtained only by studying the endometrium during the actively functioning period of life of the corpus luteum and endometrium.

Biopsies, therefore, must be taken at least four to six days prior to menstruation. This is difficult to do because of variations in time of ovulation and in length of cycles. Determination of time of ovulation by temperature shifts, vaginal smears, hormonal studies, etc., may remove some of the difficulty. If all methods of correct timing fail, repeated biopsies are necessary. One cannot, however, fail to realize the possibility of resultant infection when the uterine cavity is repeatedly invaded at short intervals. The necessity of a diagnosis must be firmly established and the need must offset this possibility before such a procedure is instituted.

Conclusions

1. There are variations in the histologic characteristics of the granulosa lutein cells in different corpora lutea and also in the same corpus luteum just prior to and during day 1 of menstruation. These variations represent normal differences in rate and extent of degeneration in these cells.

2. There are variations in the histologic characteristics of the different endometriums and also in different regions of the same endometrium just prior to and after the onset of menstruation.

3. There are also variations in the corpus luteum-endometrial relationships during this period.

4. Because of these variations, interpretations of endometrial biopsies taken near the time of onset of menstruation are particularly subject to error.

5. More accurate conclusions can be reached only by study of endometrial tissues obtained during the active functioning life of the corpus luteum and the endometrium.

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A CORRELATION BETWEEN VAGINAL SMEAR AND TISSUE DIAGNOSIS IN 1045 OPERATED GYNECOLOGIC CASES*

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THE vaginal smear as a means of detecting uterine malignancy has been well established by numerous reports[1-37] but there are none regarding its value in a hospital devoted exclusively to the care of gynecologic patients. Therefore, it has been the purpose of this study, first to determine the relative value of the vaginal smear in the discovery of cancer as compared to cervical biopsy and curettage; second, it was desired to test the practicability of the method with reference to the amount of special training the pathologist and allied personnel would need and the time they would consume in reading the smears.

Materials and Methods

Vaginal smears, prepared and stained according to the technique of Papanicolaou, were taken from in-patients at this hospital who were to be treated by surgery the following day. In addition, smears were taken from new patients in the out-patient department from whose cervices biopsies were subsequently taken. All smears were obtained before vaginal examination was performed.

All smears were interpreted by one or another of the authors, who was in complete ignorance of the clinical history and the tissue diagnosis at the time of the reading. In all cases the first smear was recorded as either positive or negative. Such interpretation on any given case was the only one used for the purpose of this study irrespective of whether or not another observer agreed with this initial diagnosis. Every field on every slide was completely examined. In suggestive smears this was done under high-power magnification, whereas it was possible to scan less suspicious smears with the low-power objective, using the high power only on questionable cells. Tissue diagnosis was the entire responsibility of one of the authors (A. T. H.) who used the accepted gross and microscopic criteria of pathologic examination.

Results

The 1,045 cases in this study were divided into three groups. The first group of 1,000 cases comprises those in which the tissue diagnosis is unquestionable. The second group consists of forty-one cases in which this diagnosis might be at variance with that of other pathologists and is, therefore, considered equivocal. The third group contains four cases in which malignancies were encountered elsewhere than in the uterus, cervix or vagina.

Group One.—In Table I are listed the various types of tissue on which is based the pathologic diagnosis. In this group of 1,000 cases there were sixty malignancies, including forty carcinomas of the cervix as shown in Table II; eighteen malignancies of the fundus (Table III); and two carcinomas of the vagina.

*Aided by a grant from the Massachusetts Division of the American Cancer Society, Inc.

TABLE I. TISSUES ON WHICH DEFINITE DIAGNOSES WERE MADE

Biopsy of cervix	152
Complete cervix (amputated)	38
Complete cervix and uterine curettings	9
Biopsy of cervix and uterine curettings	278
Uterine curettings	70
Biopsy of vagina	3
Complete uterus	448
Uterus (supravaginal portion)	2
Total	1,000

TABLE II. CARCINOMA OF THE CERVIX

Squamous carcinoma, Grade I	1
Squamous carcinoma, Grade II	29
Squamous carcinoma, Grade III	6
Adenocarcinoma, Grade II	4
Total carcinomas	40

TABLE III. MALIGNANCIES OF THE FUNDUS

Adenocarcinoma, Grade I	1
Adenocarcinoma, Grade II	8
Adenocarcinoma, Grade III	2
Adenoacanthoma	4
Carcinosarcoma	2
Mixed mesodermal tumor	1
Total malignancies	18

TABLE IV. FALSE NEGATIVE AND FALSE POSITIVE SMEARS

CASE NO.	SMEAR	PATHOLOGIC DIAGNOSIS	TISSUE
V-113	Neg.	Squamous carcinoma of cervix, Grade II	Biopsy of cervix
V-444	Neg.	Early adenocarcinoma of endometrium with hyperplasia and localized anaplasia	Complete uterus
V-461	Neg.	Early adenocarcinoma of endometrium	Complete uterus
V-797	Neg.	Adenocarcinoma of endometrium	Complete uterus
V-34	Pos.	Chronic cervicitis with erosion; menstrual endometrium	Complete uterus
V-98	Pos.	Chronic cervicitis; marked squamous metaplasia and anaplasia; late proliferative endometrium	Complete uterus
V-103	Pos.	Chronic cervicitis with erosion	Biopsy of cervix
V-202	Pos.	Chronic cervicitis with erosion and atrophy	Biopsy of cervix
V-722	Pos.	Chronic cervicitis; proliferative endometrium	Biopsy of cervix; endo. curettings
V-946	Pos.	Chronic cervicitis	Cervix (ant. lip)
V-974	Pos.	Chronic inflammation of fibrous tissue	Biopsy of vagina
V-994	Pos.	Hyperplasia and anaplasia of endometrium	Endo. curettings
V-999	Pos.	Endometrial polyp; atypical menstrual endometrium; chronic cervicitis	Biopsy of cervix; endo. curettings
V-1048	Pos.	Chronic cervicitis with erosion; squamous metaplasia; endometrial polypi	Biopsy of cervix; endo. curettings
V-556	Pos.	Chronic cervicitis; secretory endometrium	Complete uterus*

*Multiple blocks of cervix failed to locate previously diagnosed carcinoma-in-situ.

In the forty carcinomas of the cervix there were thirty-nine positive vaginal smears and one false negative smear; giving an error of 2.5 per cent. The vaginal smears from eighteen malignancies of the fundus were positive in fifteen cases. False negatives were obtained in three cases, giving an error of

TABLE V. ANALYSIS OF ERRORS

	MALIGNANCIES OF CERVIX	MALIGNANCIES OF FUNDUS	MALIGNANCIES OF VAGINA	ALL MALIGNANCIES	BENIGN CASES	TOTAL CASES
Number examined	40	18	2	60	940	1000
Incorrect diagnoses by smear	1	3	0	4	11	15
Per cent error	2.5	16.6	0	6.66	1.17	1.5

16.6 per cent. Both vaginal carcinomas had positive vaginal smears. In the total of sixty malignancies there were four false negative smears, which resulted in a total error for the malignant cases of 6.66 per cent.

In the remaining 940 cases which were declared negative by the tissue examination, there were eleven false positive vaginal smears, giving an error of 1.17 per cent. The total combined error resulting from the false negative and false positive smears is thus 1.5 per cent as shown in Tables IV and V.

Group Two.—The material in this group consists of forty-one cases in which the tissue diagnosis might be considered equivocal. This group has been

TABLE VI. CARCINOMA-IN-SITU OF CERVIX

NO.	SMEAR NO.	DATE OF SMEAR	RESULT OF SMEAR	TISSUE DIAGNOSIS	TISSUE AVAILABLE
1	V-4	11/ 1/45	Pos.	Carcinoma-in-situ, cervix	Biopsy of cervix
		12/ 4/45	Pos.	Carcinoma-in-situ, cervix	Complete uterus
2	V-65	1/28/46	Pos.	Carcinoma-in-situ, cervix	Biopsy of cervix
3	V-372	5/15/46	Neg.	Carcinoma-in-situ, cervix; senile endometrium	Complete uterus
4	V-515	7/11/46	Pos.	Carcinoma-in-situ, cervix; secret. endomet.	Biopsy of cervix, endo. curettings
		9/16/46	Neg.	Chronic cervicitis, granulation tissue	Biopsy of endocervix
		1/16/47	Neg.	Chronic cervicitis with anaplasia	Biopsy of endocervix
5	V-590	8/ 1/46	Pos.	Carcinoma-in-situ of cervix; chr. endometritis	Complete uterus
6	V-610	8/ 7/46	Neg.	Carcinoma-in-situ, cervix; squamous metaplasia	Biop. cervix; endo. curettings
		9/26/46	Neg.	Chronic cervicitis with hyperplasia	Biop. cervix
		10/10/46	Neg.	No specimen	
		1/16/47	Neg.	Chronic cervicitis with anaplasia	Biop. cervix
7	V-664	8/29/46	Neg.	Carcinoma-in-situ, cervix; prolif. endometrium	Complete uterus
8	V-766	9/25/46	Pos.	Carcinoma-in-situ, cervix	Biop. cervix
		10/17/46	Pos.	Carcinoma-in-situ, cervix	Biop. cervix
		1/ 2/47	Neg.	Chronic cervicitis; anaplasia of repair	Biop. cervix
9	V-828	10/17/46	Neg.	Carcinoma-in-situ, cervix	Complete uterus
10	V-922	11/14/46	Pos.	Carcinoma-in-situ, cervix with early invasion	Biop. cervix
		11/22/46	Pos.	Carcinoma-in-situ, cervix	Complete uterus
11	V-1037	1/ 9/47	Pos.	Carcinoma-in-situ, cervix	Complete uterus
12	V-512	7/11/46	Pos.	Carcinoma-in-situ, cervix	Biop. cervix
		7/18/46	Pos.	No specimen	
		7/30/46	Pos.	Carcinoma-in-situ, cervix (probable invasion)	Complete uterus
13	V-680	8/29/46	Neg.	Carcinoma-in-situ, cervix	Biop. cervix
		10/24/46	Neg.	Carcinoma-in-situ, cervix	Biop. cervix
		11/26/46	Neg.	Chronic cervicitis; secretory endometrium	Complete uterus

TABLE VII. PROBABLE OR POSSIBLE CARCINOMA-IN-SITU OF CERVIX

NO.	SMEAR NO.	DATE OF SMEAR	RESULT OF SMEAR	TISSUE DIAGNOSIS	TISSUE AVAILABLE
1	V-29	12/12/46	Neg.	Probable carcinoma-in-situ, cervix	Biopsy of cervix
2	V-36	1/13/46	Neg.	Possible carcinoma-in-situ, cervix	Biop. cervix, endo. curettings
		5/28/46	Neg.	Chronic cervicitis and metaplasia and hyperplasia	Complete uterus
3	V-339	5/23/46	Pos.	Probable carcinoma-in-situ and metaplasia	Biop. cervix
		6/ 6/46	Neg.	Chronic cervicitis, metaplasia and hyperplasia	Biop. cervix
		7/ 2/46	Neg.	Chronic cervicitis, metaplasia and hyperplasia	Complete uterus
4	V-340	5/23/46	Neg.	Probable carcinoma-in-situ, cervix	Biop. cervix
		6/ 6/46	Neg.	Chronic cervicitis, slight anaplasia	Biop. cervix
		9/12/46	—	Chronic cervicitis, metaplasia	Biop. cervix
5	V-356	5/28/46	Neg.	Chronic cervicitis, squam. metaplasia	Biop. cervix
		6/11/46	—	Chronic cervicitis, prob. carcinoma-in-situ	Biop. cervix
		1/ 9/46	Neg.	No specimen	
		1/ 9/47	Neg.	Chronic cervicitis	Biop. cervix (portio only)
6	V-470	6/28/46	Neg.	Possible carcinoma-in-situ, cervix	Complete uterus
7	V-528	7/17/46	Pos.	Probable carcinoma-in-situ, cervix	Complete uterus
8	V-572	7/29/46	Neg.	Probable carcinoma-in-situ, cervix	Complete uterus
9	V-625	8/12/46	Pos.	Possible carcinoma-in-situ, cervix and metaplasia	Biop. cervix, endo. curettings
		10/31/46	Neg.	Chronic cervicitis	Biop. cervix
10	V-647	8/16/46	Neg.	Probable carcinoma-in-situ, cervix and metaplasia	Biop. cervix
		11/21/46	Neg.	Chronic cervicitis, anaplasia	Biop. cervix
		12/ 5/46	Pos.	No specimen	
11	V-788	10/ 3/46	Pos.	Possible carcinoma-in-situ, cervix	Complete uterus
12	V-790	10/ 3/46	Neg.	Probable carcinoma-in-situ, cervix	Biop. cervix, endo. curettings
		12/ 5/46	Neg.	Chronic cervicitis	Biop. cervix
13	V-852	10/24/46	Neg.	Chronic cervicitis, prob. carcinoma-in-situ	Biop. cervix
		10/31/46	Neg.	Chronic cervicitis and paraleukokeratosis	Biop. cervix
		12/ 9/46	—	Chronic cervicitis, hyperplasia and anaplasia	Complete uterus

TABLE VIII. CARCINOMA-IN-SITU OF ENDOMETRIUM

NO.	SMEAR NO.	DATE OF SMEAR	RESULT OF SMEAR	TISSUE DIAGNOSIS	TISSUE AVAILABLE
1	V-14	12/11/45	Pos.	Adenocarcinoma-in-situ, endometrium	Complete uterus
2	V-328	5/28/46	Neg.	Carcinoma-in-situ, endometrium and polyp	Biop. cervix, endo. curettings
		7/29/46	—	Endometrial hyperplasia and anaplasia	Complete uterus
3	V-335	5/23/46	Neg.	Carcinoma-in-situ, endometrium and hyperplasia	Complete uterus
4	V-364	5/29/46	Neg.	Endometr. polyp with carcinoma-in-situ, hyperplasia and anaplasia	Complete uterus
5	V-776	9/26/46	Neg.	Carcinoma-in-situ, endometrium	Complete uterus
6	V-831	10/18/46	Neg.	Carcinoma-in-situ, endometrium	Complete uterus
7	V-861	10/26/46	Neg.	Carcinoma-in-situ, endometrium	Complete uterus

further divided into twenty cases that were diagnosed as *definite* carcinoma-in-situ of the cervix and endometrium respectively (Tables VI and VIII) and twenty-one cases in which there was judged to be in one or the other of these tissues either *probable* or *possible* carcinoma-in-situ (Tables VII and IX). This apparent indecision is the result of an attempt to segregate all such suspicious cases for study and follow-up in order that the true position of carcinoma-in-situ may be more clearly defined. We term them equivocal because many pathologists are in disagreement as to the validity of this diagnosis even when definitely made.

TABLE IX. PROBABLE OR POSSIBLE CARCINOMA-IN-SITU OF ENDOMETRIUM

NO.	SMEAR NO.	DATE OF SMEAR	RESULT OF SMEAR	TISSUE DIAGNOSIS	TISSUE AVAILABLE
1	V-12	12/11/45	Neg.	Possible carcinoma-in-situ; anaplasia	Complete uterus
2	V-247	4/25/46	Neg.	Chronic cervicitis and squamous metaplasia	Biop. cervix
		8/22/46	Neg.	Possible carcinoma-in-situ, endometrium; cervical polyp and chronic cervicitis	Biop. cervix; endo. curettings
3	V-417	6/12/46	Neg.	Probable carcinoma-in-situ	Complete uterus
4	V-465	6/19/46	Neg.	Probable carcinoma-in-situ and hyperplasia	Biop. cervix; endo. curettings
		6/28/46	Neg.	Radium reaction, endometrium	Complete uterus
5	V-711	9/10/46	Neg.	Possible carcinoma-in-situ and hyperplasia	Complete uterus
		10/31/46	Neg.	No specimen	
6	V-753	9/13/46	Neg.	Possible carcinoma-in-situ and hyperplasia; endometrial and endocervical polyps	Complete uterus
7	V-821	10/15/46	Neg.	Probable carcinoma-in-situ; endo. and cervical polyps	Complete uterus
8	V-933	11/18/46	Neg.	Probable carcinoma-in-situ	Complete uterus

Table VI shows the data in thirteen cases of carcinoma-in-situ of the cervix. It will be noted that in eight instances at least one vaginal smear is positive and in five cases all those taken were negative. It is noteworthy that in Cases 4 and 8 the original biopsies showed carcinoma-in-situ of the cervix with positive vaginal smears, while subsequent biopsies and vaginal smears were negative. Was the malignant tissue completely removed by biopsy?

In Case 6, in which on four occasions the smears were called negative, the tissue diagnosis was also negative on the last two of three biopsies. Hence disagreement was with only the first surgical specimen. The carcinomatous lesion in this case involved mainly the basal layers, suggesting that positive cells may not have reached the surface or for some other reason were prevented from desquamating. Again, did biopsy remove all the affected area?

In Case 7 the vaginal smear was negative and although the original tissue diagnosis was carcinoma-in-situ of the cervix, it was necessary to cut blocks from the entire cervix in order to locate the tiny malignant lesion. The single vaginal smear in this case immediately preceded hysterectomy and was made after the initial biopsy.

In Table VII thirteen cases are listed in which a diagnosis of *probable* or *possible* carcinoma-in-situ of the cervix was made. In only four of these a positive vaginal smear was found. In two of them it may be seen that the smear later became negative and that the tissue diagnosis also became negative, again suggesting complete removal of the pathologic area.

In Case 10 the last vaginal smear, positive, was taken late in the study. It will be of interest to note what the next biopsy of this cervix will show.*

The cases in Table VIII consist of seven patients in which a definite diagnosis of adenocarcinoma-in-situ of the endometrium was made. Only one positive smear was found in this group. This indicates the difficulty of an accurate smear diagnosis in this type of lesion, which is not surprising since this lesion that is not considered valid by many qualified pathologists, tends to be deeply situated and is thus less apt to cast off cells directly into the uterine cavity. It will be noted that even in frank carcinomas of the endometrium there was less correlation with the vaginal smear.

Table IX gives the data from eight cases in which a diagnosis of *probable* or *possible* carcinoma-in-situ of the endometrium was made. No positive smears were encountered, a fact which is again not surprising in view of the questionable nature and location of the lesion. In Case 2 the patient has since become pregnant. This would indicate a fairly healthy endometrial status, although the possibility of an early carcinoma's having been completely removed by curettage cannot be ruled out.

The smear results from all cases of carcinoma-in-situ are shown comparatively in Table X.

TABLE X. CARCINOMA-IN-SITU RESULTS

		NUMBER OF CASES	POSITIVE SMEARS	NEGATIVE SMEARS
Definite	Cervix	13	8	5
	Endometrium	7	1	6
Questionable	Cervix	13	4	9
	Endometrium	8	0	8

Group Three.—The four incidental malignancies in this group are not included with the others because their diagnoses do not seem to be applicable to the vaginal smear technique. Pathologic examination in these cases revealed lesions respectively of the Fallopian tube, bladder, urethra and vulva. Positive smears in all four indicate that malignant cells from such sources may be carried into the vagina.

Discussion

The value of the smear as compared to tissue diagnosis is manifest in the tabulation of errors shown in Table V. Since the method in actual daily application would undoubtedly provide the observer with clinical information which the authors purposely avoided, its accuracy could be reasonably expected to increase, largely by the avoidance of false positive readings. It is further significant that only one of the four false negative readings (V-797) occurred because malignant cells were initially unrecognized although present, whereas the other three have been repeatedly re-examined without the discovery of malignant cells, thus indicating an irreducible error inherent in the

*From comparison of the corresponding smears and tissue specimens in these cases it may be that in many instances the first biopsy either completely removed the carcinomatous area or instigated a more intense reparative reaction which resulted in normal healing. This would imply that the carcinoma-in-situ is a result of prolonged subminimal stimuli with abortive attempts at healing which go astray. When a more violent stimulus is provided, such as that incident to biopsy, a more normal repair process ensues and results in the formation of normal tissue.

method. In view of these facts the method has been found eminently satisfactory for detecting malignancy in the cervix and vagina, but less so in the endometrium.

Attainment of this degree of accuracy required training of personnel and a considerable investment in time devoted to the reading of smears. For the former, each of the examiners, previously experienced in tissue diagnosis, after studying the available literature[1-37] spent about two weeks under the intensive tutelage of Mrs. Ruth Graham and her assistants at the Vincent Laboratory of the Massachusetts General Hospital. Such is the training required.

The time consumed in reading varied tremendously and the process at best was much longer and far more tedious than the corresponding tissue examination. It may be roughly estimated that average smears required from fifteen to twenty minutes apiece while in some particularly difficult smears it would require up to two hours. Under conditions other than those stipulated for ourselves, a smear of this type could be labelled "suspicious" and new smears requested. In many cases a second smear might not be so difficult as the first. It must again be emphasized that for the purpose of this study only one smear was examined and that by only one observer, with a subsequent definite negative or positive diagnosis being made. Furthermore, every field of every smear was inspected. Many laboratories would probably not spend this much time, but such a practice would lower the accuracy of the method, especially in early lesions. On several occasions the diagnosis in this study was made from one or two characteristic cells when no other signs were present on the slide. It must be remembered that the technique is actually a random sampling of only a portion of a pool of cells desquamated from all parts of the genital tract.

The study has shown the method to be highly accurate and that it is possible to develop a vaginal smear department of the pathology laboratory within one year. It has proved unexpectedly valuable in the study of early carcinoma and carcinoma-in-situ as well as in the diagnosis of more advanced cases.

Summary

1. A study has been made of 1,045 vaginal smears and the corresponding uterine, cervical and/or vaginal tissue sections. In 1,000 of these cases sixty malignancies of the uterus, cervix or vagina were encountered. Forty-one cases of definite or questionable carcinoma-in-situ were discussed separately.

2. In forty cases of carcinoma of the cervix, thirty-nine were found to have positive smears and one did not; giving an error of 2.5 per cent. In eighteen malignancies of the uterus, fifteen smears were positive and three were negative; giving an error of 16.6 per cent. Two carcinomas of the vagina were encountered and both had positive smears with no error.

3. The total error of positive cases called negative is 6.66 per cent. In the remaining 940 cases with negative tissue sections there were eleven false positive vaginal smears; giving an error of 1.7 per cent. The total combined error of false positive and false negative smears is thus 1.5 per cent.

4. Four incidental malignancies were encountered including one each from the bladder, urethra, vulva and Fallopian tube.

5. Eight positive and five negative smears were encountered in thirteen carcinomas-in-situ of the cervix. Only one positive smear was found in seven carcinomas-in-situ of the endometrium.

6. Four positive smears were encountered in thirteen questionable carcinomas-in-situ of the cervix. No positive smear was found in eight questionable carcinomas-in-situ of the endometrium.

Conclusions

The vaginal smear method is an accurate and valuable adjunct to a gynecologic clinic. Although time-consuming, it can be satisfactorily carried out in a pathology laboratory equipped and staffed with the necessary trained personnel.

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THE RELATIONSHIP BETWEEN SEX HORMONES AND EXPERIMENTALLY INDUCED TUMORS IN RATS*

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WHILE the etiology of cancer is obscure, the number of agents indicated as factors in carcinogenesis is extensive. Various substances have been incriminated in the causation of cancer as a result of the accumulation of a vast amount of circumstantial evidence noting the prevalence and repeated occurrence of malignant neoplasms in different occupational trades. For instance, it was shown in the investigation of human occupational cancers that certain coal tar derivatives were carcinogenic. Thus, the classical example of scrotal carcinomas in chimney sweeps demonstrated the role of occupational hazards in cancer.[1] Although the inciting factor could only be suspected, it was the epochal work of the Japanese workers that established the role of coal tar in carcinogenesis when applied locally in the production of skin cancer.[2] Later, extractions of the carcinogenic principle led to the isolation of a chemically pure carcinogenic compound of the 1:2 benzanthracene series, in particular 3:4 benzpyrene,[3, 4] the only potent carcinogenic compound found to be present in coal tar. The manner in which tumorigenesis is initiated by the coal tar derivative has not yet been determined.

In view of the experimental production of carcinogenesis by certain hydrocarbons of the pentacyclic aromatic groups, it has been suggested that malignant neoplasms arising spontaneously in the organism may likewise be induced by the endogenous formation of cancer-producing hydrocarbons arising from the abnormal metabolism of cholesterol or of the bile acids. The eventual demonstration of a degradation product, methylcholanthrene, from a naturally occurring constituent of the organism, bile acids, gave support to the hypothesis that potent carcinogens may be evolved in the body.[5]

Further proof that endogenous substances, such as methylcholanthrene, may be related to or arise from substances occurring naturally in the organism, is the apparently striking fact that the 1:2 benzanthracene derivatives belong to the cyclopentane ring group characteristic of the naturally occurring sterols and sex hormones.[6] The role of the sex steroids, particularly estrogens, in inciting abnormal growth and neoplasia of the generative tract of the female, while long suspected, has only been proved experimentally in the past decade or two. The evolution of the concept that estrogens are important in the initiation of carcinogenic changes in the female reproductive tract is interesting to follow. The first line of evidence was observed early at the turn of the century when bilateral oöphorectomy was first performed as an ameliorating measure in carcinoma of the breast.[7] While this procedure has since been frequently performed and is still carried out by some modern surgeons, it has been generally abandoned. Recurrent waves of enthusiasm

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for the operation[8, 9] nevertheless set in only to be discarded again and relegated to the limbo of therapeutic dreams. It appears, then, that long before the discovery and identification of estrogenic hormone, the ovary was thought to be an agent responsible in some way for the development of certain malignancies of the breast and genital tract.

Credence was lent to the assumption of an ovarian-breast tumor relationship by the findings of Leo Loeb who reported in 1907[10] that the incidence of spontaneous breast cancer in certain strains of mice was very high in the female, nil in the male. Furthermore, in 1916[11] Loeb and his co-workers demonstrated that ovariectomy at an early age (i.e., before six months) prevented or greatly reduced the incidence of mammary carcinoma in strains of mice which normally had a high incidence. If spaying, however, was performed after the eighth month there was no appreciable reduction in incidence. This work was confirmed and extended by Cori.[11a] It remained for Lacassagne to show that mammary cancer could be induced in male mice following injections of estrogens if the strain employed belonged to one in which the females had a high incidence of spontaneous mammary cancer.[12] His observations permitted the conclusion that the genetic factors for cancer, present in both males and females, became operative only after the mammary glands had grown in response to estrogenic stimulation.

While the importance of estrogens as carcinogenic agents in certain small animals was definitely established by Lacassagne's experiments, it must not be forgotten that the hereditary or the genetic susceptibility must exist. Slye, Little, Andervont, and others later demonstrated the role of genetics alone and in combination with other factors in the role of spontaneous cancer in mice.[13-17] Other nongenetic factors have also been incriminated as playing important roles in spontaneous mammary cancer. For instance, it was found that when females of a high cancer strain were bred with males from a low cancer strain, the female offspring had a high incidence of mammary cancer. When, however, the females of a low cancer strain were bred with males from a high cancer strain, the female offspring showed a low incidence of mammary cancer. Later, Bittner[18-20] showed that this nongenetic element in mammary carcinogenesis is the milk factor. If, for example, the young from cancer susceptible mothers are fostered by cancer resistant mothers, the incidence of subsequent mammary cancer is reduced, and vice versa.

From the experimental work quoted, it seems that mammary cancer is caused by the conjoined action of three factors:[19, 20] (1) estrogens, (2) a nongenetic agent transmissible to the offspring from the mother's milk, and (3) a genetic factor which controls to some extent the susceptibility of the mammary tissue to neoplastic changes by the other two factors.

The factors just enumerated do not apply to carcinogenesis of other primary and secondary sex organs. Cervical cancer could be produced in mice if estrogen therapy was prolonged for at least a year at a time.[21-24] It was noted that cervical cancer could be induced in strains of mice resistant to mammary cancer. These mice, however, exhibited poor tolerance to the chronic estrogenic treatment at levels effective for cervical carcinogenesis.[22] The "milk factor," so important in determining the incidence of mammary cancer, apparently had no relation to incidence of cancer of the cervix following administration of estrogens.[24] In this connection it must be recalled that cervical cancer, unlike mammary cancer, does not appear spontaneously in mice.

In view of relative similar chemical configuration of the carcinogenic hydrocarbons and the sex steroids and their respective roles in carcinogenesis, the following studies were undertaken to establish the possibility of synergism exist-

ing between these two general groups in the initiation of carcinogenesis. Observations are presented on the influencing effect of various endocrine steroids on tumors induced by methylcholanthrene or benzpyrene when these latter substances are administered either subcutaneously or directly into the uterus. Experimental findings are also recorded on the influence of various endocrine preparations administered chronically not only on the production of chemically induced tumors, but also on other organs of the injected animal. The effect of the different steroid hormones on subcutaneously transplanted sarcomas is also described.

Procedure

As a base line for our studies and to learn some fundamentals about the problem thirty young white rats, commercially obtained, were employed in preliminary experiments. Varying quantities of methylcholanthrene in dosages from 10 to 50 mg. were administered subcutaneously in one to several injections. In all, circumscribed sarcomas developed within three to six months at the site or sites of injection (Fig. 1). The sarcomas did not metastasize. The tumors grew to relatively enormous size (Fig. 1). Occasionally ulcerations developed superficially. The rats were sacrificed 8 to 12 months after the start of the experiment. In several rats methylcholanthrene was injected directly into the uterine horn with a view toward inducing local tumorigenesis in the uterus. The horn was tied off and threads passed through various parts to traumatize the tissue. Estrogens or estrogen and progesterone were then administered in chronic doses for several months, along with occasional subcutaneous injections of methylcholanthrene. The subcutaneously administered methylcholanthrene served a twofold purpose: (1) to further influence the proliferative propensities of the sex-related organs, and (2) to act as control to the methylcholanthrene introduced into the uterus. Sarcomas developed at the sites of subcutaneous injection of methylcholanthrene, but no sarcomas were observed to develop in the uterus in any instance.

A typical protocol is that on rat No. 8 (methylcholanthrene injected into the right horn) presented in Table I.

TABLE I

1/14/39	10 mg.	methylcholanthrene injected into right uterine horn (horn tied).
1/16/39	80 r.u.	
1/18/39	80 r.u.	
1/21/39	50 r.u.	
1/24/39	50 r.u.	
1/27/39	60 r.u.	
1/30/39	70 r.u.	
2/ 6/39	70 r.u.	
2/10/39	80 r.u.	
2/13/39	120 r.u.	Estrogenic Substance (also 20 mg. methylcholanthrene
2/19/39	130 r.u.	subcutaneously into right dorsum)
2/20/39	130 r.u.	
3/ 7/39	425 r.u.	
3/15/39	400 r.u.	
3/23/39	365 r.u.	
4/ 8/39	100 r.u.	
5/ 4/39	40 r.u.	(also 50 mg. methylcholanthrene
5/ 7/39	40 r.u.	subcutaneously into left dorsum)
	2,290 r.u.	over period of 5 months.
8/ 4/39	Tumor 3 by 3 cm. in size on right dorsum—appeared about 7/15/39	
10/ 1/39	Second tumor present on left dorsum—appeared about 9/20/39	
Autopsy performed one year after start of experiment.		

Table I summarizes the substances administered to this rat. The tumors at the sites of injection were large. No breast tumor development was discernible. The rat was autopsied twelve months after start of the experiment. The right uterine horn was distended (Fig. 2). Histologic examination revealed a pyometrium and squamous cell metaplasia of the uterine mucosa of the right horn (Fig. 3). Sections of the ovaries, liver, kidney, lung, and left horn of the uterus failed to show any noteworthy changes. Cervical sections revealed marked epithelial hyperplasia. Histopathologic study of the tumor tissue revealed spindle shaped cells growing autonomously with marked cellular derangement, frequent and bizarre mitotic figures and multinucleated giant cells. Large, thin-walled arterioles were observed throughout the section. This rat received over 2,200 r.u. of estrogenic substance over a period of five months.

Fig. 1.—Methylcholanthrene induced sarcoma.

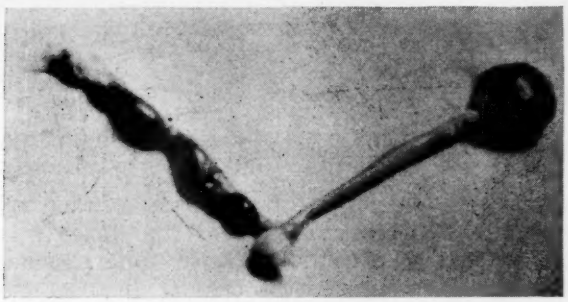

Fig. 2.—Note distended right uterine horn twelve months after intrauterine administration of methylcholanthrene.

It was apparent from our preliminary studies that methylcholanthrene could produce sarcomas in every instance at the subcutaneous site of injection. However, when introduced into the uterine horn and in spite of accompanying trauma and prolonged administration of estrogens, tumorigenesis of the uterine horn could not be obtained other than squamous cell metaplasia and some suggestive precancerous lesions of the cervix. It was decided to continue with a more systematic study employing benzpyrene along with various endocrine preparations. This study followed several directions:

A). The effect of implantation of pellets of benzpyrene into the uterine horn on tumorigenesis and the influence of various hormonal pellets implanted into the opposite horn.—

Studies were undertaken to determine the direct tumorigenic effect of benzpyrene upon the uterine mucosa. Accordingly, pellets of benzpyrene were implanted into the uterine horn. One to two pellets weighing 10 to 15 mg. (total) were implanted into the left uterine horn. The influencing effects of the sex steroids were also ascertained by direct implants of 13 to 17 mg. pellets of testosterone, progesterone, and estradiol into the lumen of the opposite uterine horn.

Control animals received only pellets of benzpyrene. Animals of both groups were ovariectomized prior to implantation of the pellets. At the time of implantation, the uterine horns were threaded with black silk proximal and distal to the pellets in order (a) to maintain adequately the pellets and prevent their extrusion, and (b) to provide an additional means of irritating the uterine mucosa and establish thereby a more "fertile" ground upon which the carcinogenic agents might act.

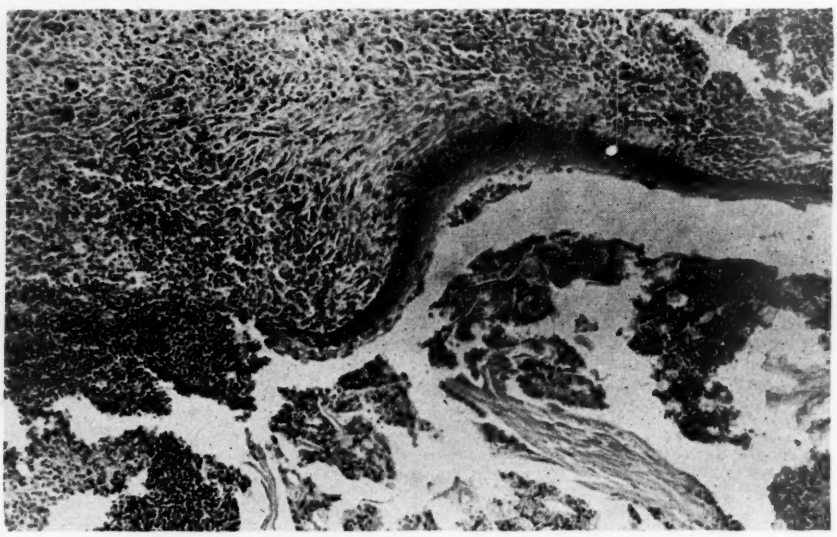

Fig. 3.—Pyometria and squamous cell metaplasia following intrauterine administration of methylcholanthrene (×125).

Daily vaginal smears, via pipette lavage, were taken throughout the experimental period. Frequent cornification of the smear was observed in the animals receiving implants of estradiol pellets. Smears made from other animals in the remaining group showed the typical diestrus smear characterized by a predominance of leucocytes in a typically mucous medium. All animals were autopsied one hundred eighty days after implantation of pellets.

In no instance, in either the experimental or control series, were intrauterine pellets of benzpyrene productive of any neoplastic changes. Some of the steroids produced marked gross and morphologic changes (Table II). The pellets of progesterone produced no striking anatomical changes and in every case were entirely absorbed in the period of one hundred eighty days. The only discernible effect of the pellets of testosterone was to bring about a diminution in the size of the hypophysis of the implanted animal. Sixty to 75 per cent by weight of the pellets were absorbed. In contrast, marked changes were produced in the animals receiving intrauterine implantation of

pellets of estradiol (Table II). The uterine weight was increased threefold over that of the controls. There was also marked hypertrophy of the adrenal glands and both hypertrophy and hyperplasia of the hypophysis. Morphologically, the changes in the pituitary gland were shown to be predominantly ones of chromophobic activity. Fifty to 75 per cent by weight of the pellets of estradiol were absorbed after one hundred eighty days.

TABLE II. BENZPYRENE IMPLANT INTO LEFT HORN OF UTERUS (WITH HORMONE IN OTHER HORN (RIGHT). ANIMALS AUTOPSIED 180 DAYS AFTER IMPLANTATION

TREATMENT	UTERUS (MG.)	ADRENAL (MG.)	PITUITARY (MG.)	THYROID (MG.)
Benzpyrene	255 (3)*	39 (3)	17.2 (3)	13.3 (3)
Benzpyrene and progesterone	221 (3)	45 (3)	17.8 (3)	12.0 (3)
Benzpyrene and testosterone	235 (2)	35 (2)	13.2 (2)	13.5 (3)
Benzpyrene and estrogen	734 (1)†	67 (2)	71.7 (2)	11.5 (2)
Control-normal‡	507	55	13.0	13.0
Control-castrated‡	135	58	13.5	14.3

*Figures in parentheses indicate number of animals.

†One uterus, large and bulky, with numerous adhesions, could not be dissected free. Weight estimated between 500-700 mg.

‡Control data represent average weights of 25 rats.

B). Effect of benzpyrene injected subcutaneously and the influence of estrogens or estrogens and desoxycorticosterone on the benzpyrene induced tumors.—The sarcoma-inducing qualities of benzpyrene were ascertained by injecting a total dose of 20 mg. of benzpyrene in sesame oil over a period of forty days. The benzpyrene was administered subcutaneously every second day in 1 mg. doses contained in 0.05 c.c. sesame oil. The influence of estradiol dipropionate and combined injections of both estradiol dipropionate and desoxycorticosterone acetate upon the induction of sarcoma by benzpyrene was likewise determined. Estradiol dipropionate (0.025 mg.) and desoxycorticosterone (0.25 mg.) were administered in 0.05 c.c. of sesame oil every second day. The endocrine preparations did not appear to accelerate or diminish the rate of growth of the benzpyrene induced tumors. Sarcomas developed at the site of injection of benzpyrene in all the animals within ninety to one hundred twenty days. No demonstrable difference in relation to time of appearance, rate of growth and microscopic appearance of the tumor was observed in the sarcomas produced by benzpyrene and those observed in animals receiving benzpyrene and steroid preparations. The sarcomas, however, varied greatly in size in each individual group and ranged from 10 to 92 Gm. in weight. In some animals the tumors attained 50 per cent of the weight of the animal. Grossly these growths were sharply circumscribed, well encapsulated and showed no gross or microscopic evidence of metastases. Microscopically, the sarcomas were identical to those induced by methylcholanthrene (Fig. 8).

C). Transplantation of benzpyrene-induced tumors and the influence of various hormones on transplantability.—The tumors from all three groups of animals described above were readily transplantable and the transplantations were carried for three to six generations (Figs. 4 and 5). The tumors were transplanted into adult female rats weighing between 200 to 250 Gm. within three to five minutes after autopsy. The donor animals were killed by ether asphyxiation. The tumors were dissected from the animal, weighed, and divided into small rectangular portions about 2 by 4 by 10 mm. in size and weighing 50 to 75 milligrams. Two or three tumor slices were implanted subcutaneously into the scapular region of the recipient animals. The animals implanted were divided into two groups: (1), the experimental, received daily injections of some endocrine preparation; (2), the uninjected control group.

The relationship of various endocrine preparations to the growth of transplanted sarcomas was tested by administration of estradiol dipropionate, desoxycorticosterone acetate, progesterone, testosterone propionate and thiouracil to the animals receiving the transplants of the sarcomatous tissue. The following doses of these preparations were administered every second day in 0.05 c.c. of sesame oil in the case of the steroid hormones, and in 0.1 c.c.

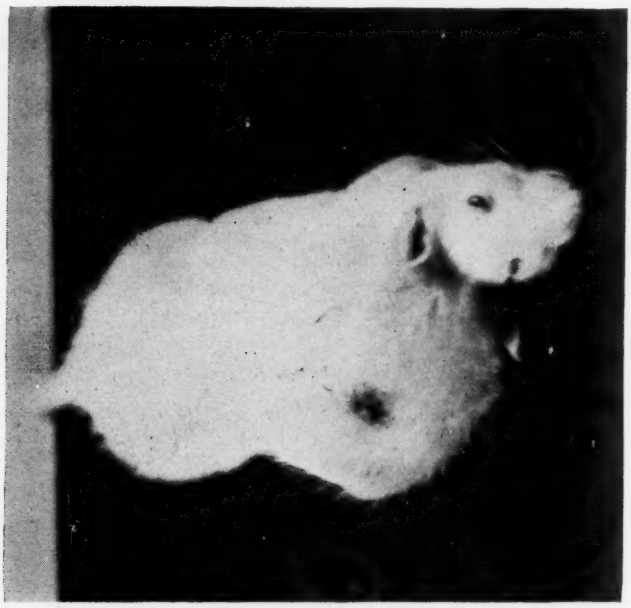

Fig. 4.—Growth of sarcoma thirty-six days after transplantation of benzpyrene induced sarcoma (third generation).

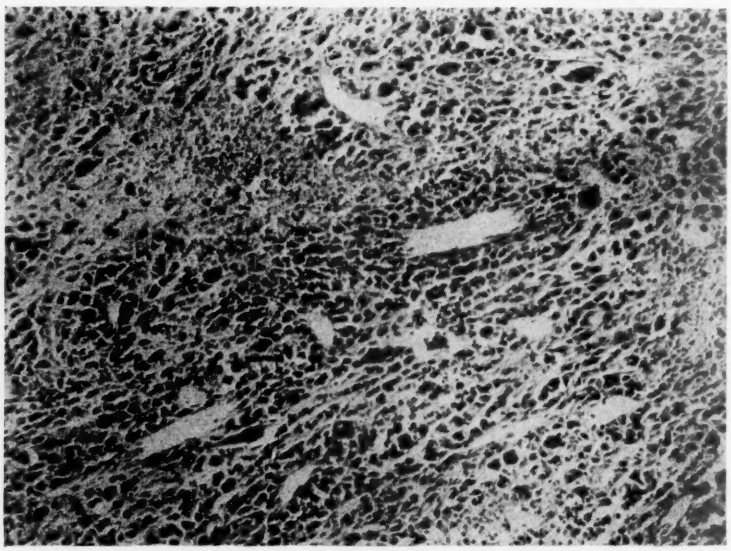

Fig. 5.—Histologic section of growth of sarcomatous tissue transplanted five weeks previously. Tissue transplanted from benzpyrene-induced sarcoma. Sarcoma weighed 24 grams. Note characteristic large, thin-walled capillaries, multinuclear giant cells and cellular derangement.

water for the thiouracil; estradiol dipropionate .025 mg., desoxycorticosterone acetate 0.5 mg., progesterone 0.5 mg., testosterone propionate 0.25 mg., thiouracil 10 mg. The percentage of successful transplantations ranged from 79 per cent for the controls to 40 per cent in the animals receiving progesterone.

In addition to treating the animals with various hormones at the time the transplants were made, the effects of pretreatment with estradiol dipropionate, testosterone propionate, desoxycorticosterone, and progesterone upon the growth of the transplanted sarcoma was observed. The recipient animals in this group received endocrine therapy two to four months before the tumor transplants were made with therapy continuing after implantation. The dosages of these preparations employed in the pretreatment phase of the experiment were similar to those described above. In this latter group of animals there was no evidence to show that the steroids administered in this manner enhanced

Fig. 6.—Chromophobic adenoma induced in pituitary gland after 7.5 months of estrogen administration.

TABLE III

TREATMENT	DAYS TREATED	OVARY	ADRENAL	THYMUS	UTERUS	THYROID	PITUITARY	TUMOR	PER CENT OF TUMOR TAKE
Estrogen	167.90 ± 3.86* (24)†	26.40 ± 0.82 (24)	68.70 ± 0.98 (24)	73.00 ± 1.57 (22)	622.50 ± 6.71 (23)	16.20 ± 0.78 (24)	120.40 ± 4.73 (24)	44.80 ± 2.31 (12)	50%
Progesterone	121.60 ± 16.86 (5)	49.60 ± 4.41 (5)	88.60 ± 9.68 (5)	101.40 ± 14.18 (5)	351.20 ± 29.18 (5)	18.20 ± 1.05 (5)	14.50 ± 1.15 (5)	155.00 ± 3.57 (2)	40%
Testosterone propionate	92.30 ± 8.92 (6)	51.80 ± 11.96 (6)	47.70 ± 3.04 (6)	122.20 ± 13.83 (6)	270.50 ± 8.04 (6)	16.00 ± 0.56 (6)	10.70 ± 0.28 (6)	134.00 ± 1.88 (3)	50%
Desoxycorticosterone acetate	68.80 ± 3.89 (8)	54.40 ± 3.06 (8)	76.50 ± 1.39 (8)	86.30 ± 9.36 (8)	337.50 ± 23.50 (8)	16.80 ± 0.52 (8)	13.10 ± 0.22 (8)	109.70 ± 7.29 (6)	75%
Control	80.00 ± 2.05 (33)	62.40± 1.11 (33)	72.40 ± 0.67 (33)	94.20 ± 1.65 (33)	352.70 ± 6.07 (33)	16.00 ± .095 (33)	11.60 ± 0.10 (33)	79.90 ± 1.76 (26)	79%

*Standard error.
†Figures in parentheses indicate the number of animals.

or inhibited the rate of growth of the transplanted sarcoma over and above that observed when therapy was initiated simultaneously with transplantation.

The data, while meager in some experiments, indicate upon analysis that estradiol had an inhibiting effect on the rate of growth of the transplanted sarcomas (Table III). In addition to a decreased incidence of successful takes as compared to the controls, there was also a significant reduction in weight of the transplanted sarcoma in the estrogen treated animals over that observed in the control groups. The weight of the sarcomas in the animals treated with

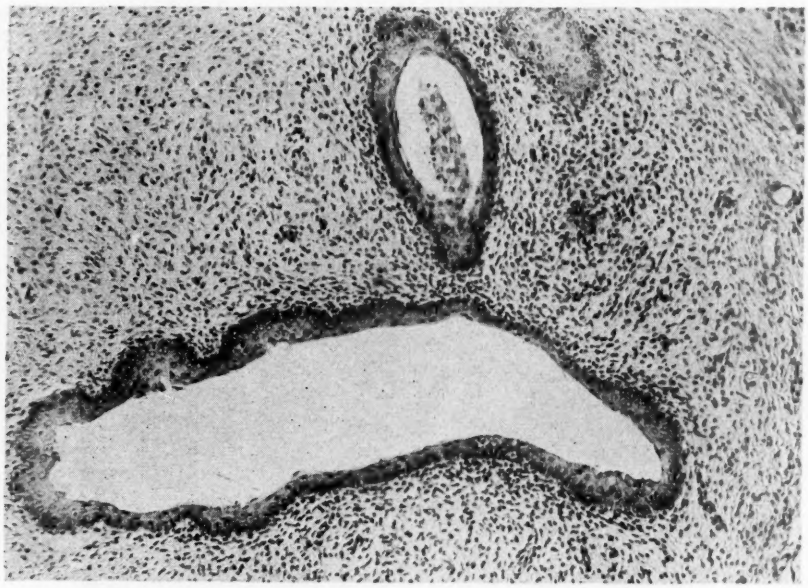

Fig. 7.—Squamous cell metaplasia of endometrium of uterus after administration of estrogen for five months (×145).

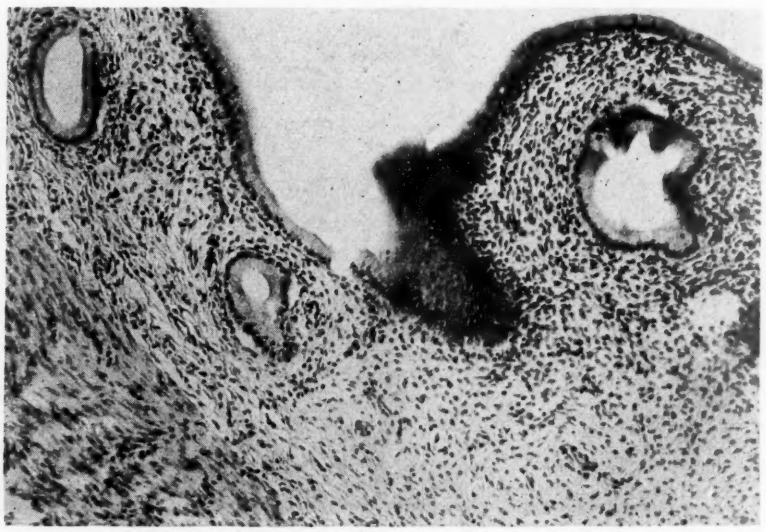

Fig. 8.—Area of anaplasia of endometrium of uterus in rat receiving estrogens for 5.5 months. Note the abrupt change from columnar epithelium to an area of squamous cell type. Many mitotic figures are to be noted in this area which is suggestive of anaplastic change.

estradiol dipropionate was only 57 per cent that of the neoplasms of the control animals. While administration of progesterone, testosterone propionate, and desoxycorticosterone acetate caused a 34 to 94 per cent increase in weight of the sarcoma over that attained in the control rats, there was a decreased incidence in tumor takes in those animals receiving progresterone and testosterone propionate. In contrast to the animals receiving intrauterine implants of pellets of progesterone and estrogen, subcutaneous administration of estradiol dipropionate in oil caused no adrenal hyperplasia, while progesterone in oil caused hypertrophy of questionable significance. Testosterone propionate injections resulted in a reduction in size of the adrenal glands. Estradiol, as has been reported, resulted in marked hypertrophy of the pituitary gland (Fig. 6). The hypertrophy of the hypophysis was due mainly to hyperplasia of the chromophobic elements forming in many instances a chromophobic adenoma. Estrogens also caused a marked hypertrophy of the uterus and in many cases squamous cell metaplasia of the mucosa was observed (Fig. 7). Metaplasia, however, was never observed with chronic administration of progesterone, desoxycorticosterone acetate or testosterone propionate. In one instance a localized area of anaplastic change in the uterine mucosa was found (Fig. 8). Definite malignant changes in the breasts were observed in only one rat receiving estrogens, although many animals showed proliferative changes indicative of cystic changes in the acini of the breast.

Discussion

From an analysis of our studies it appears that the estrogenic hormone is a strong proliferative hormone and that methylcholanthrene and benzpyrene applied directly to the uterine mucosa could not induce out and out malignant changes in the uterine horn, despite administration of chronic doses of estrogenic substance. In this respect Castellano and D'Amour did obtain occasional malignancies in their experiments when pellets of methylcholanthrene were implanted into the uterus.[25] However, no discussion of the microscopic picture of the neoplasms was presented, nor were the malignancies described. Their period of observation, however, was longer—a minimum of one year. In addition, workers from the same laboratory reported a statistically significant hastening of the appearance of the subcutaneous methylcholanthrene-induced tumors under the influence of pregnancy urine and pregnant mares serum (PMS).[26] PMS appeared to sustain a greater effect. In our study, aside from epithelial metaplasia of the endometrium and epithelial stimulation of the cervix, no carcinomatous changes of the reproductive tract were observed. Geschickter was able to produce carcinoma of the breast in rats by injection of 200 gamma over 100 days.[27] This dosage was far greater than which we used.

There can be no doubt that estrogens, administered over a relatively long period of time to certain experimental animals, are capable of inducing malignant changes in a substratum hereditarily susceptible to cancer. An impression has been created, however, that what strictly applies to animal experimentation also applies to man. Thus the implications of the neoplastic tendencies of estrogenic or estrogenic-like substances in certain susceptible animals have led, and properly so, to the cry for caution in the empirical use of long-continued, massive dosage of estrogens clinically. Although it has

been shown that estrogens play some role in the production of a cancerous state of the mammary and occasionally the uterine (cervical) tissue of mice susceptible to cancer, estrogenic substances play little or no part in mice refractory to cancer and none in larger animals.[28] Evidence of carcinogenic action of estrogens in the human female is meager and at times is only suggestive. Sporadic reports have shown that estrogens or estrogenic activity may be indicted in the pathogenesis of certain cases of breast or uterine carcinoma.[29-31] These reports are of necessity poorly controlled and the conclusions could well be challenged. In this respect it is interesting to speculate concerning the doses employed in the rat and the comparative dosage in the human. On the basis of the dosage given to the rat in this experiment the amount to be given to the human, calculated in the table below, would be in line of such excessive doses as 6.5 mg. administered every second day for a period of 14.5 years (Table IV).

TABLE IV. DOSE OF ESTRADIOL RELATIONSHIP BETWEEN THE RAT AND THE HUMAN

	LIFE SPAN	WEIGHT	DOSE Q 2ND DAY	TIME ADMINISTERED
Rat	3 years	0.25 kg.	25.0 gamma	8.0 months
Human	65 years	65.00 kg.	6.5 mg.*	14.5 years†

*Dose based on that given to rats and on weight relations of rat to human.
†Time estimated on total time of hormone administration to rats and relation of life span of rat to that of human.

Another line of evidence to consider when evaluating the role of estrogens in the etiology of neoplasms is the contradictory results observed in those cases of breast carcinomas that had been treated with stilbestrol. Synthetic estrogens have been reported to bring about temporary retardation or partial regression of the neoplastic growth.[32] These observations have been confirmed.[33] Thus it was shown that of a total number of 69 patients under the age of 57 given stilbestrol for advanced breast cancer, 43 did not improve while some showed spectacular improvement. Stilbestrol administered to 52 patients over 58 years of age resulted in improvement in 17 cases and spectacular improvement in six or seven cases. In this latter group in some patients there was complete disappearance of the fairly advanced disease.[34] These findings have been substantiated recently in a 91-year-old woman with a breast carcinoma.[35] The carcinoma subsided with no evidence of swelling after six months of treatment with daily doses of 3 mg. of diethylstilbestrol. It has also been shown that secondary sarcomatous deposits in the lung of a young woman disappeared completely two years after stilbestrol treatment had been instituted.[36]

Summary

The effect of various steroid hormones upon the induction of carcinogenesis by methylcholanthrene and benzpyrene was studied. Subcutaneous and intrauterine administration of the carcinogenic agents was made by injecting either oil solutions or suspensions of the carcinogen in lard and by implantation of compressed pellets of benzpyrene. No neoplastic changes were observed in rats receiving intrauterine application of either one of the coal tar derivatives

alone or in combinations with the steroid hormones. The sarcomatous inducing effect of subcutaneously administered benzpyrene was not influenced by the simultaneously administered steroids. Transplantation of the benzpyrene induced sarcomas appeared to be influenced by administration of hormones. Animals receiving estradiol exhibited sarcomas smaller in size than those observed in the control animals. On the other hand, progesterone, testosterone and desoxycorticosterone acetate appeared to enhance the growth of the transplanted sarcomas. Data is also presented on the effect of steroid substances on the production of neoplastic changes in the endocrine glands and accessory reproductive organs of the rat.

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RELATIONSHIP BETWEEN ERYTHROCYTE SEDIMENTATION RATE, SLUDGED BLOOD, AND PLASMA PROTEINS DURING PREGNANCY*†

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AMONG the several factors which have been associated with changes in erythrocyte sedimentation rate are these: Fähreus[1] noted increased rouleaux formation and higher plasma fibrinogen and globulin values in blood from patients with increased sedimentation rates; and it was demonstrated subsequently, by Monaghan and associates,[2] that sedimentation rate depended upon constituents contained within blood plasma. In fact, in vitro studies by Coburn and Kapp[3] showed a quantitative relationship between an increased speed of sedimentation and amounts of added fibrinogen or globulin. Gray and Mitchell[4] confirmed this observation, using protein fractions prepared electrophoretically by the Tiselius method, and observed that the addition of purified albumin reduced the speed of sedimentation. That both anemia[5] and increased temperature, in vitro,[6] will change sedimentation rate is well recognized.

Of additional importance are the studies of Hinselmann,[7] Linzenmeier,[8] and Krogh,[9] who reported "stasis" within the fingernail capillaries of normally pregnant and toxemic patients, "stasis" being more pronounced in the latter. More recently, Knisely and co-workers[10-14] have made comprehensive studies of intravascular changes under normal, experimental, and pathologic states. According to them, the findings in normal unanesthetized men and women consist of: an absence of intravascular agglutinations of red blood cells or adherence of white cells to vessel walls, presence of a "laminated" or "streamlined" flow, absence of a plasma "leak" through small vessel walls, and a rate of flow fast enough so that individual red cells cannot be recognized at 48 to 90 diameters of magnification. Contrawise, in various experimental and pathologic states, microscopic agglutinations of blood cells occur within venules and arterioles, and this tendency to form intravascular cell masses causes the blood to circulate, in certain instances, as a thick "sludge." It has been further shown that the state of the circulating blood, as based upon conjunctival observations, is a statistically valid sample of the circulating blood throughout the entire body.

The purposes of this paper are (1) to report the presence of "sludged blood" in women during both normal uncomplicated pregnancy and during pathologic pregnancies, (2) to report that the masses of agglutinated red cells are larger in certain of the pathologic conditions examined than in the uncomplicated pregnancies, (3) to point out probable relationships between (a) the

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intravascular agglutinations of the blood, (b) the increased in vitro sedimentation rates of blood from these patients, and (c) changes in the concentrations of certain plasma protein fractions.

Material

A total of 52 pregnant and nonpregnant subjects were selected for study. These included 21 whose pregnancy was normal and 23 whose pregnancy was complicated, 16 with toxemia, four with thrombophlebitis and infection, two with acute hemorrhagic shock, and one with ectopic pregnancy. Nonpregnant controls numbered eight.

Equipment consisted of a Leitz dissecting microscope of 48 diameters magnification mounted on a colposcope stand and a Shahan opthalmic lamp with usual adjustments.

Method

Patients were observed in the supine position from the right side, the light beam being directed through the lateral aspect of the right palpebral fissure. By elevating the right upper lid, with the examiner's left hand, and instructing the patient to deviate vision toward the left, it was possible to focus the Leitz instrument on the lateral bulbar conjunctiva with the right hand. The size of intravascular masses and the degree in reduction of rate of flow were evaluated in fine, medium, and large venules and in arterioles. This was arbitrarily designated as +, ++, +++, or ++++, and, on the basis of these direct microscopic observations, an estimate was made of the sedimentation rate. Venous blood was then obtained, without stasis, and collected in tubes for analysis. Sedimentation rates were read in a Wintrobe tube on heparinized blood at ten-minute intervals for one hour, the cell volume being obtained from the same tube after centrifugation for the Plass-Rourke[15] corrected rate. Precautions to maintain constant room temperautres and erect sedimentation tubes were observed during all readings.

Fibrinogen and total serum proteins were determined on the interferometer by a method described by Dieckmann.[16] Albumin and globulin fractionization was obtained by a method described by Pellemer and Hutchinson,[17] which gives results closely approximating those obtained by the Tiselius electrophoretic procedure.[17]

Results

1. *Observations by Microscopy.*—

These numbered 103, seventy-seven of which are tabulated with simultaneously obtained sedimentation rates and plasma protein values (Tables I, II, III, and IV).

a. *Nonpregnant controls:* In none of six female subjects studied whose sedimentation rates were below 24 mm./hour was any intravascular agglutination of the blood observed. Occasionally, a "laminated flow," as described by Knisely and associates,[14] was seen in the large venules of some eyes. However, two other patients, whose diagnoses were pelvic inflammatory disease and generalized carcinomatosis, had large, easily observable agglutinations within venules and arterioles, a reduced rate of blood flow, and, in some vessels, temporary cessation of flow; and, as anticipated, their sedimentation rates were high (Table I).

b. *Normal pregnancy:* "Sludged blood," consisting of intravascular agglutinations of erythrocytes and reduced rates of flow with temporary cessation (of flow) in some vessels, was observed in all subjects with sedimentation rates of 33 mm./hour or more. "Sludge" was more easily seen in those patients

TABLE I. NONPREGNANT CONTROLS

PATIENT	PLASMA PROTEINS MG./100 C.C.					SEDIMENTATION RATE MM./HR.				SLUDGE			
										VENULES			
	TOTAL SERUM PROTEIN	FIBRINOGEN	GLOBULIN	ALBUMIN	A/G	WESTERGREN CALCULATION	UNCORRECTED VALUE	HEMATOCRIT	PLASS-ROURKE	FINE	MEDIUM	LARGE	ARTERIOLES
P. R.	6.7	0.28	2.3	4.4	1.9	2	10	41	0.17				
V. E.	7.5	0.22	3.1	4.4	2.4	6	7	41	0.12				
R. L.	6.9	0.31	3.0	3.9	1.3	13	20	44	0.36				
H. H.	7.4	0.34	3.1	4.2	1.4	15	17	46	0.37				
M. O.	6.7	0.38	3.2	3.5	1.1	20	24	45	0.43				
L. W.	5.8	0.30	3.2	2.6	0.82	21	–	–	–				
Average:	6.8	0.30	3.0	3.8	1.5	14.5	15.6	43	0.29				
379352	6.3	0.73	3.2	3.1	0.91	46	59	34	0.89	++++	+++	+++	+
340038	6.4	0.89	–	4.9	–	67	56	35	0.86	+++	+++	+++	+

TABLE II. NORMAL PREGNANCY

OBSERVATIONS	PLASMA PROTEINS MG./100 C.C.					SEDIMENTATION RATE MM./HR.				SLUDGE			
										VENULES			
	TOTAL SERUM PROTEIN	FIBRINOGEN	GLOBULIN	ALBUMIN	A/G	WESTERGREN CALCULATION	UNCORRECTED VALUE	HEMATOCRIT	PLASSROURKE	FINE	MEDIUM	LARGE	ARTERIOLES
9	5.3-6.5	0.27-0.43	2.3-2.8	3.0-3.8	0.9-1.7	9-32	11-34	31-44	0.20-0.57				
Average:	5.94	0.34	2.6	3.3	1.3	18	22	37	0.34				
5	5.0-6.8	0.34-0.50	1.8-3.2	2.9-3.6	1.0-1.7	15-43	26-42	30-39	0.59-0.63	+ to ++	+ to ++		
Average	5.74	0.42	2.4	2.7	1.4	28	37	35	0.61				
7	5.4-6.9	0.33-0.64	2.4-3.4	2.8-3.7	0.9-1.5	12-46	32-50	31-40	0.53-0.73	++ to +++	+ to ++	+	
Average:	6.2	0.44	2.8	3.3	1.2	29	41	38	0.66				

with an increased sedimentation rate. In fact, it seemed that the size of the cell aggregates increased progressively in direct ratio with the hourly uncorrected sedimentation rate. "Sludge" was detected most readily in fine venules, where it had the appearance of a string of beads; next in medium-sized venules, where it had the appearance of granules; and least readily in large venules, appearing there as larger clumps. "Sludge" was not observed in arterioles during normal pregnancy, almost certainly because the masses were small and the blood flow very rapid. The largest cell masses, and the greatest reduction in rates of flow, were seen in those patients who were near term, in labor, or early in the puerperium (Table II).

c. *Pathologic pregnancy; pregnancy toxemia:* A noticeable narrowing of arterioles could be detected in most patients. In addition, intravascular agglutinations and reduced flow rates were observed. The sizes of masses comprising the "sludge" were larger, the rate of flow considerably more decreased, and cessation of flow more prolonged, as compared with normal pregnancy. One patient (M. L. 323886) deserves special comment. This Case, POG1, unregistered, and six and one-half months pregnant, was admitted in coma with a history of one convulsion. Immediately after the third convulsion, observations disclosed arteriole constriction. The venules, in certain areas, were segmentally constricted in such a way that short segments contained blood and intervening portions were empty. Blood flow through these vessels had ceased, and was not reestablished for several minutes. In larger venules the blood flow appeared to be very slow although no agglutinations could be detected.* During the two hours following sedation and intravenous hypertonic solutions the constricted vessels dilated, flow through them was re-established, and individual agglutinations could be detected. The hematocrit reading changed from 50 per cent, immediately after the third convulsion, to 45 per cent two hours later, and subsequently to 37 per cent some time afterward. The sedimentation rates during this period were 15 mm. (immediately after a convulsion), and 38, 43, 31, and 39 mm./hour during subsequent treatment. No other convulsions occurred. Delivery followed premature artificil rupture of the membranes and the administration of solution of posterior pituitary. The puerperium was uncomplicated. Observations of the sedimentation rate conducted on a second eclamptic (L. E. 379384) showed similar changes. The rates in this case were 32 mm. (immediately after a convulsion), and 45 and 47 mm. during and after treatment; the hematocrit was 38, 35, and 31 per cent, respectively (Table III).

Thrombophlebitis and infection: Microscopic conjunctival examination disclosed large intravascular agglutinations within fine, medium, and large venules and in arterioles. In addition, stasis[19] and a few minute thrombosed venules were seen. Sedimentation rates were unusually high in these patients.

Hemorrhagic shock: Three instances of severe hemorrhagic shock were observed, two in the same patient. The first (E.W. 376643), P4G5, aged 42 years, was admitted at thirty-eight weeks in shock of two hours' duration from severe hemorrhage due to placenta previa. Distinct, irregular, rigid agglutinations were observed within venules of the conjunctiva. These masses moved slowly, and reversal of flow for short intervals was frequent. Agglutinations were visible also in arterioles, and the rate of flow in them was slowed. Following transfusion of 4,200 ml. of blood the patient's condition improved, and there was no visible "sludge." However, two hours after a cesarean hysterectomy the "sludge" again became visible and the sedimentation rate became elevated. The patient was discharged well on the sixtieth postoperative day, the puer-

*Knisely and Bloch[18] have observed similar concentration in one eclamptic patient, and they interpret absence of visible agglutination to vessel leak which packs the masses tightly together so that edges of individual masses cannot be seen.

TABLE III. TOXEMIA OF PREGNANCY

OBSERVATIONS	PLASMA PROTEINS MG./100 C.C.					SED.MENTATION RATE MM./HR.				SLUDGE			
										VENULES			
	TOTAL SERUM PROTEIN	FIBRINOGEN	GLOBULIN	ALBUMIN	A/G	WESTERGREN CALCULATION	UNCORRECTED VALUE	HEMATOCRIT	PLASSROURKE	FINE	MEDIUM	LARGE	ARTERIOLES
3	5.1-5.9	0.30-0.55	1.5-2.5	3.4-3.6	1.4-2.4	8-47	23-40	37-45	0.30-0.65	+ to +++	+		
Average:	5.5	0.42	2.0	3.5	1.8	25	29	40	0.47				
27	3.9-6.2	0.31-0.56	1.9-4.0	1.5-3.4	0.5-1.8	11-51	34-58	26-45	0.49-0.92	++ to ++++	++ to ++++	+ to +++	
Average:	5.2	0.45	2.7	2.4	0.92	39	50	34	0.75				
7	4.8-6.3	0.31-0.57	1.7-3.5	2.3-3.4	1.0-1.8	18-56	51-57	29-38	0.69-0.86	++ to ++++	++ to ++++	++ to ++++	+
Average:	5.4	0.47	2.6	2.8	1.3	40	52	34	0.81				

TABLE IV. PATHOLOGIC PREGNANCY

PATIENT	PLASMA PROTEINS MG./100 C.C.					SEDIMENTATION RATE MM./HR.				SLUDGE			
										VENULES			
	TOTAL SERUM PROTEIN	FIBRINOGEN	GLOBULIN	ALBUMIN	A/G	WESTERGREN CALCULATION	UNCORRECTED VALUE	HEMATOCRIT	PLASS-ROURKE CORRECTION	FINE	MEDIUM	LARGE	ARTERIOLES
						Shock and Hemorrhage							
E. W. 376643	5.6	0.53	3.1	2.5	0.8	53	52	38	0.84	+++	+++	+++	
A. B. 124582	5.6	0.25	2.4	3.2	1.3	5	24	31	0.35				
	4.8	0.23	2.1	2.7	1.3	4	29	35	0.44				
	5.5	0.31	2.7	2.8	1.0	18	51	36	0.80	++++	++++	+++	+
						Thrombophlebitis and Infection							
E. W. 376643	5.3	0.52	2.9	2.5	0.9	48	62	31	0.90	++++	++++	+++	++
G. F. 385319	6.3	1.25	4.2	2.1	0.5	164	56	37	0.89	++++	++++	++++	++
G. G. 164236	6.3	0.49	2.8	3.5	1.3	39	44	38	0.71	++	++	+	
A. W. 377805	6.8	0.28	3.7	3.1	0.8	18	57	32	0.84	+++	+++	++	+
						Ectopic Pregnancy							
E. G. 385385	5.9	0.37	1.9	3.9	2.0	15	16	44	0.30				

perium being complicated by a pelvic thrombophlebitis. The second case (A. B. 124582), P9G12, aged 37 years, was admitted at twenty weeks gestation for therapeutic aboriton because of hypertensive vascular disease. An estimated 1,500 ml. hemorrhage occurred during dilation and curettage. Microscopic examination commenced during the operation disclosed large intravascular masses of red cells, and markedly reduced rates of flow in all small venules. Transfusions of whole blood (1,500 ml.) restored blood volume and an intrauterine pack controlled hemorrhage. Two days later a second hemorrhage followed removal of the uterine pack. Profound shock resulted. Microscopic examination disclosed constricted veins but no visible "sludge," and the sedimentation rate was only 24 mm./hour. However, following transfusion of whole blood and curettage, intravascular agglutinations and visible reduction in rate of flow occurred; the sedimentation rate became 51 mm./hour. The remainder of the hospital stay was uncomplicated.

Ectopic pregnancy: One patient (E. G. 385385) was observed who had a provisional diagnosis of acute pelvic inflammatory disease. This case had no visible "sludge" and a low erythrocyte sedimentation rate. An ectopic pregnancy with left hematosalpinx was discovered during laparotomy (Table IV).

2. *Sedimentation rate.*—

Estimates of sedimentation rate, based on conjunctival observations, closely approximated the measured, uncorrected, hourly values (Table V). In addition, microscopic findings as to the size of the masses correlated with a sliding scale of sedimentation rates (Table VI). Values were higher at term, in labor, or during the puerperium, and highest in infections. In addition, the sedimenta-

TABLE V. RELATIONSHIP OF E.S.R. TO AMOUNT OF INTRAVASCULAR "SLUDGE"

PATIENT	SEDIMENTATION RATE 1 HOUR	VENULES			ARTERIOLES
		SMALL	MEDIUM	LARGE	
7 controls*	7-20				
379352	59	+++	+++	+++	+
340038	56	+++	+++	+++	+
M. M. 21296	23	+			
I. N. 381922	24	+	+		
S. L. 124582	24				
A. B. 383217	26	+	+		
E. L. 271273	29				
S. L. 124582	29				
G. B. 357426	32	++	+	+	
M. V. 388369	34	++	+	+	
M. C. 158661	38	+	+		
M. T. 378782	40	+++	+		
E. R. 375466	43	+++	++	++	
M. V. 388369	48	+++	+++	+++	
G. L. 375409	48	+++	+++	++	+
A. S. 376640	50	+++	+++	++	
R. R. 381772	51	+++	++	++	
R. R. 381772	51	+++	+++	++	
M. R. 376091	51	+++	+++	++	+
M. R. 376091	51	+++	+++	++	+
S. L. 124582	51	++++	++++	+++	+
A. S. 376640	53	+++	+++	++	
M. V. 388369	54	+++	+++	++	
M. F. 378732	55	+++	+++	++	
M. F. 385319	56	+++	+++	+++	++
M. M. 193700	57	+++	+++	++	+
M. W. 376643	62	++++	++++	+++	++

*Nonpregnant controls.

tion rates from patients with pregnancy toxemia tended to be higher than those obtained during normal pregnancy. There was close correlation with plasma fibrinogen values, less with albumin, globulin, or A:G ratio, and no relationship with total serum proteins (Figs. 1, 2, and 3). The Plass-Rourke corrected rates (computed on the percentage of hourly sedimentation as related with the hematocrit reading) related to plasma fibrinogen figures (Fig. 4). The Westogren calculation for sedimentation rate, computed from plasma protein fractions by the formula, Sedimentation Rate = 140.4 fibrin. % + 6.22 glob. % + 6.09 alb. % – 25.5, yielded inconsistent results.

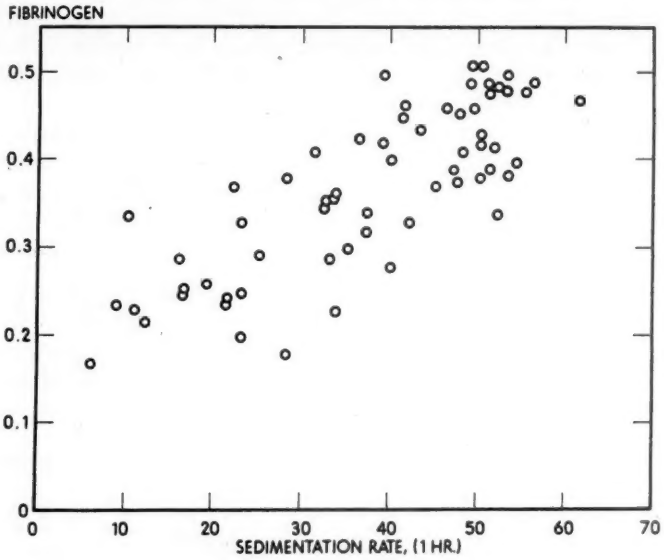

Fig. 1.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Fibrinogen and sedimentation rate.

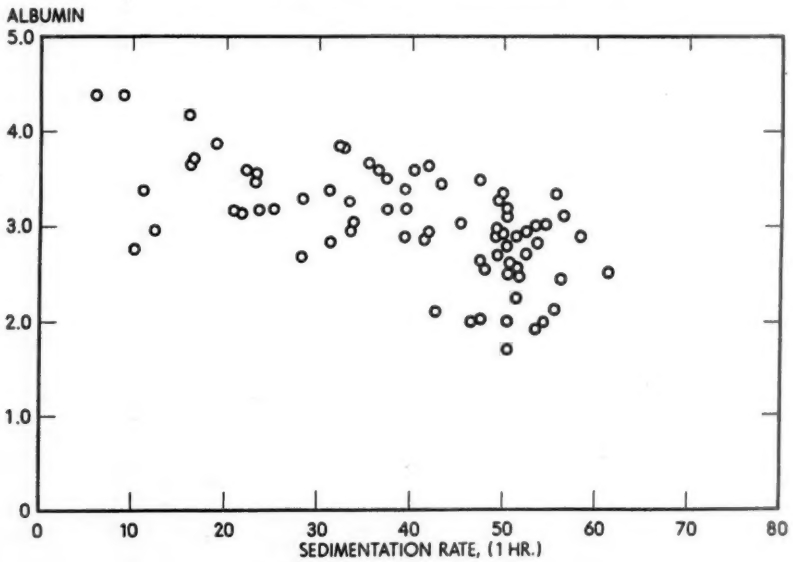

Fig. 2.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Plasma albumin and sedimentation rate.

Comment

This study correlates the presence of intravascular agglutinations of erythrocytes and reduced rates of blood flow during pregnancy with the erythrocyte sedimentation rate, and the latter with plasma fibrinogen and albumin levels. Bøth Fähreus[20] and Linzenmeier[8] suggested such a relationship, their observations being based upon opthalmoscopic examinations of the retina, upon fingernail microscopy, and upon artificially produced stasis in extremities. However, the

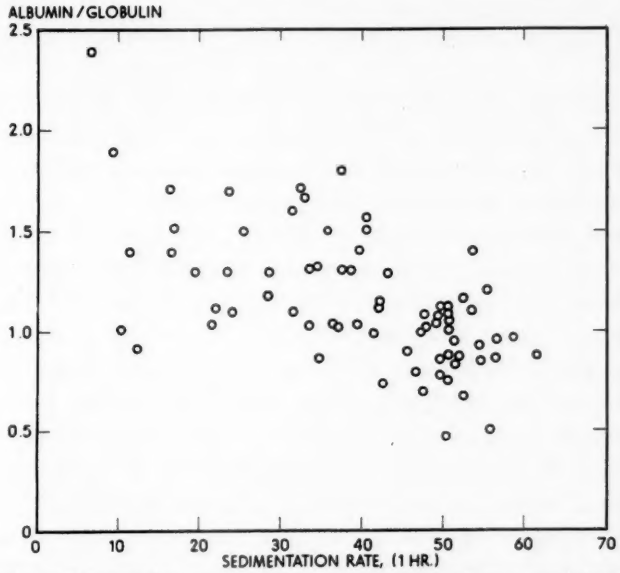

Fig. 3.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Albumin globulin and erythrocyte sedimentation rate.

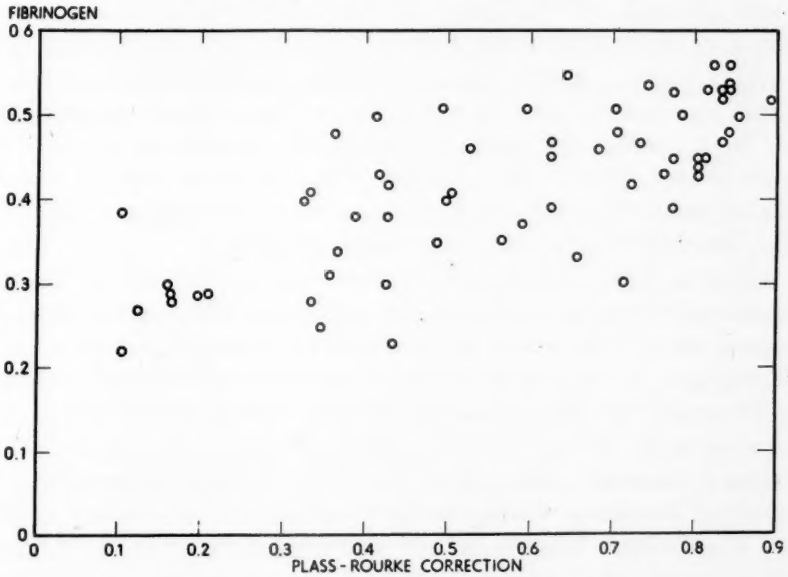

Fig. 4.—Erythrocyte sedimentation rate, sludged blood, and plasma proteins during pregnancy. Fibrinogen and Plass-Rourke correction.

TABLE VI. RELATIONSHIP OF E.S.R. TO THE ESTIMATED VALUE

NUMBER PATIENTS	AVERAGE SEDIMENTATION RATE 1 HOUR	ESTIMATED VALUE
12	17	below 20
5	24	20-30
4	42	30-40
5	49	35-45
6	42	40-50
3	53	45-55
7	51	50-60
4	53	55-65
1	62	60-70

Knisely-Bloch technique for intravascular observations in the human being, as used in this study, offers much improvement over the previously used methods since an uninterrupted, clear, and detailed examination of entire vessel segments and surrounding tissue spaces can be easily obtained.

It would seem that intravascular "sludge" was related to rouleaux formation, a phenomenon already associated with the erythrocyte sedimentation rate.[1] Rouleaux formation was originally attributed to an attraction between negatively and positively charged erythrocytes,[21, 22] but more recent investigations suggest cell stickiness or cohesiveness as an important mechanism. Just what constitutes stickiness between cells is not well understood. According to Ponder,[23] intercellular cohesiveness is probably a property of surface tension. Lecompte Du Nouy[24] studied the later phenomena extensively and concluded that larger protein molecules in solutions tend to concentrate at interfaces (as monolayers), thus producing a more viscous substance. Knisely, and associates,[13] while studying sludged blood, observed and photographed under darkfield illumination in vitro a thick, glassy, cottony precipitate (probably a protein) present between and around all the red cells of each agglutinated clump.

It should be stressed, however, that rouleaux formation differs, by definition, from an intravascular agglutination of cells (or "sludge"). The former consists of an in vitro piling-up of red cells, like coins, one on another; the latter of in vivo intravascular cell aggregates wherein erythrocytes are held together at all angles to each other.[14] Nevertheless, it would appear that both phenomena relate to an increased cellular cohesiveness, and the nature of the substance causing this should become an object for much research.

The addition of hyaluronic acid, a tissue polysaccharide, to citrated blood will increase sedimentation and rouleaux, while hyaluronidase, a tissue enzyme, has a reverse effect. However, the addition of either desoxyribonucleic acid, gelatin, fibrinogen, or hyaluronic acid to normal citrated blood causes a considerably increased erythrocyte sedimentation. And Meyer and co-workers[25] suggest that probably all highly assymetrical molecules of large size will increase sedimentation. It would seem that the basic problem concerning "sludged blood" does not consist in finding artificial methods of producing it in vitro as rouleaux. The problem is more that of altering "sludge" in the living animal.

In the experimental animal "sludged" blood follows trauma. In fact, photographs[14] of minutely injured areas on monkey omentums reveal intra-

vascular masses forming the instant circulating blood contacts crushed tissues. Conversely, bleeding experiments, conducted within limits of safety on human beings, did not cause the formation of sludge within the first half hour.[26] The two instances of hemorrhagic shock in this report substantiate these observations. In the first case (E. W. 376643) hemorrhagic shock had existed for two hours prior to hospitalization, sufficient elapsed time for considerable hemodilution and, as a result, an elevated sedimentation rate (because of anemia), and an increased rouleaux and "sludge." However, in subsequent examination of this patient, as well as of the other patient in hemorrhagic shock (A. B. 124582), it is significant that operative trauma preceded the appearance of intravascular "sludge."

Gray and Warner[28] have produced and photographed "sludged" blood in guinea pigs by injecting electrophoretically prepared beef fibrinogen, and Dieckmann[27] has observed a temporary alleviation of "stasis" within fingernail capillaries following intravenous hypertonic glucose solution. In the present study two patients received intravenously 25 and 60 Gm., respectively, of electrophoretically purified albumin. There was a transitory decrease in the amount of "sludge" and speed of sedimentation. In addition, the effect of intravenous 5 per cent saline solution and human plasma was studied. And two patients were observed under dicumerol medication. None of these altered permanently this "sludge" or the sedimentation rate to a significant degree.

In two eclamptics hemoconcentration was associated with a lowered sedimentation rate. This observation agrees with those[29] who suggest that the removal of plasma in vitro interferes with rouleaux formation, so that rouleaux becomes smaller and sedimentation rate slower. In addition, the consistently increased "sludge" in pre-eclamptic toxemia, as compared with normal pregnancy, and the obvious plasma "leak" in convulsive toxemias, suggests that circulatory physiology sometimes becomes sufficiently disturbed in the former to the point of anoxia, and in the latter results in the loss of plasma to the tissues; in short, a cause and effect relationship. Such a sequence of events occurs experimentally, at least, with "sludged blood."[12, 14]

Summary

"Sludged" blood, as characterized by intravascular agglutinations and reduced rate of flow, is found in normal and pathologic pregnancy and in some nonpregnant women. This phenomena is apparently related to an increased erythrocyte sedimentation rate which, in turn, correlates with plasma fibrinogen and albumin values. It is possible to make estimates of erythrocyte sedimentation rate from the microscopic conjunctival observations.

During shock "sludge" is apparently related to subsequent hemodilution or to the accompanying operative trauma, rather than to an acute loss of blood. During thrombophlebitis and infections the size of intravascular masses is particularly increased. During preconvulsive toxemias "sludge" is increased, and during eclampsia anoxia could explain the rapid loss of plasma to the tissues.

The authors are indebted to Dr. Wm. J. Dieckmann, Dr. M. M. Knisely, and Dr. E. H. Bloch for advice concerning this study.

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Discussion

DR. M. H. KNISELY.—Some new terms have been used here. "Sludged blood" is not yet in common use in medicine. Dr. Edward H. Bloch and I worked at the University of Tennessee College of Medicine in Memphis with Drs. Stratman-Thomas and Eliot for two years studying sludged blood in monkeys infected with knowlesi malaria. Later we found intravascular agglutination of the blood of human beings diagnosed by practicing physicians as having about 40 pathologic conditions and diseases. (Cf. Knisely, Stratman-Thomas, Eliot and Bloch, 1945; and Knisely and Bloch, 1942, 1945). Further, when working with Dr. Lathan Crandall and his colleagues in Memphis we found precipitation and agglutination of the blood of traumatized dogs, and working with Dr. Lester Dragstedt, Dr. Franklyn Brooks and Louise Warner we have found agglutination of the blood of animals and people following burns. In the laboratory we have been interested in finding the kinds of damage caused by the precipitation and/or agglutination of the circulating blood to a circulating sludge.

Words and sentences do not clearly tell what we mean by "sludging of the blood." Hence, at this point I would like to show a short motion picture taken through the microscope which shows the course of some of the events in traumatic shock. I think that what it shows is closely related to the changes in the blood which Dr. Odell and colleagues have found following separation of the placenta. (The motion picture was presented; it showed that in traumatized tissue the blood flowing through the traumatized areas changes from a fluid to a stiffly precipitated and agglutinated sludge [Cf. Knisely, Eliot and Bloch] 1945.) When this process has been going on in large enough areas of tissue for a long enough time, all of the circulating blood is changed to a stiff mucklike sludge. After the blood is changed to a sludge the masses of which the sludge is composed resist passage through the long cone-shaped arterioles, capillaries, and postcapillary venules. In consequence, the rates of flow

through tissues become too slow, the tissues become anoxic, and the endothelium of the postcapillary venules becomes anoxic, and in consequence begins to leak, letting fluid out through the vessel walls into the tissues. The stagnant anoxia of the vessel walls (a) permits loss of fluid into the tissues, (b) causes hemoconcentration of the circulating blood, and (c) causes decreasing circulating blood volume. The film showed visible aspects of the above). This film is not a finished motion picture ready for public distribution; it is an assembly of laboratory records pieced together to demonstrate these processes until we have time to make a long careful cinema record of all the stages of these processes as we have observed them in experimental traumatic shock.

With any given arterial pressure, venous pressure, and degree of dilatation of arterioles, capillaries, and venules, the degree of reduction of the rates of flow through capillaries caused by sluding of the blood is proportional to a combination of two mechanical factors: (1) the the sizes of the masses of agglutinated blood cells, and (2) the internal rigidities of these masses. The larger and more rigid the more they resist passage through small vessels, particularly the long, narrow, cone-shaped arterioles, and thus reduce the rates of flow of blood through the capillary networks of all tissues. Thus the changing of the blood to a sludge can, depending upon the mechanical consistency of the sludge, cause many different degrees of slowed flow, endothelial anoxia, leaking of vessels, hemoconcentration, and reduced venous return. Accumulating laboratory evidence indicates clearly that when the masses become large and rigid enough this series of mechanisms becomes the direct cause of death (Cf. Knisely, Stratman-Thomas, Eliot, and Bloch, 1945).

One other pathologic consequence of changing the blood to a sludge is a little more complicated, and takes a little more time to present. When India ink is injected into a frog, each particle of the ink receives a coating of a glassy precipitate, probably protein derived from the blood plasma. This coating material acts as an opsonin; it sticks to and then is instantly ingested (with its contained ink) by the phagocytic lining cells of the liver sinusoids. In monkeys with malaria the red cells which are coated by glassy precipitates also stick to the linings of hepatic sinusoids and are instantly ingested, and coated red cells are also phagocytized in the spleen and bone marrow. The rate of phagocytosis of coated red cells can be much higher than anyone might suspect; in one monkey with malaria, in which we determined the rates of phagocytosis by doing consecutive closely spaced parasite counts, we found that the animal phagocytized one-third of all his circulating blood in three hours. It seems probable that in this monkey all the conditions necessary for ingestion of coated red cells were optimal, thus giving very high rates of phagocytosis. But it is important to know that one major effect which can follow agglutination of the blood is the rapid phagocytic destruction of coated circulating blood cells, and that the rate of phagocytosis of coated red cells can be so rapid as to cause an anemia and/or a decrease in the animal's circulating blood volume. In response to the decreased blood volume, the arterioles of many tissues are shut off for much longer periods than they are during normal phases of normal physiology. It seems quite probable that this series of mechanisms may be occurring in many human pathologic conditions and diseases. It is of course now necessary to find out whether all the different kinds of coatings on red cells which can stick them together in agglutinated masses are equally phagocytozable, or to find out the conditions under which each kind of coating is phagocytizable.

Often in animals the tendency of anoxic, leaking vessels to cause a hemoconcentration is counterbalanced by the tendency of the phagocytosis of coated red cells to cause reduced red-cell counts. As fluid and red cells are both being lost, the red-cell count of the circulating blood stays normal while, insidiously, these factors both contribute to reduction of blood volume, venous pressure, and venous return (Cf. Knisely, Stratman-Thomas, Eliot and Bloch, 1945).

DR. JOSEPH L. BAER.—The subject matter of the main paper is distinctly over my head. It happens that a quarter of a century ago I was interested, and Dr. Reis with me, in both sedimentation rates and capillary microscopy. We labored long hours at Michael Reese Hospital studying sedimentation rates and developing what we felt were fairly good repro-

ductions of the work of Linzenmeier and of the only other man in the United States who had done that work, namely Friedlander of Detroit. We were able to convince ourselves that the sedimentation rate was exactly what it was held out to be, namely, a delicate test for certain clinical conditions such as infections, degenerative diseases, and malignancies. We were able to satisfy ourselves that as compared with sedimentation in normal people, these other conditions hastened the settling of the red cells. It took us a considerable period to convince our colleagues in our department of gynecology and obstetrics that the sedimentation rate was a proper adjunct in the study of the patient, even though we were able to demonstrate that it was a somewhat more delicate prognostic as well as diagnostic test than the ordinary leucocyte count which up to that time has been the sole laboratory criterion. It took ten years before clinicians in other branches of medicine paid any attention to the sedimentation rate, namely, those in the field of tuberculosis, the pediatricians, and finally the internists. Now the sedimentation rate is a definitely accepted part of the procedure in the study of such patients.

A quarter of a century ago our facilities consisted of an ordinary microscope, a very low power objective, and a miniature light source. The finger of the patient was mounted on a tongue depressor and held with adhesive. A drop of immersion oil was placed over the clean nailbed. The light was obtained with a cystoscope bulb and the current provided by a dry cell battery. Even with that primitive set-up we were able to see some of the things which everyone should see, the terminal capillary loops with efferent and afferent arms. It was entirely possible to see the erythrocytes moving through these loops. In the healthy individual these loops are as regular as a palisade fence, whereas in chronic cardiac disease, chronic nephritis, and other types of circulatory disturbances, there are changes which result in all sort of distortions many of which were named in the literature of that day. In the severe toxemias we thought we were able to demonstrate angiospasm, which was of some clinical significance.

The correlation of the sedimentation rate with studies in capillary microscopy and the work presented here has advanced so far beyond these early studies that it demonstrates conclusively that the clinician cannot carry out such fundamental studies, yet cannot carry on the practice of medicine without this kind of study. It is gratifying to see that the talents of biochemists, of physiologists, and of anatomists are being applied to this field of medicine which I think is exceedingly important and with which every one of you can make himself at least basically familiar by looking at your own or someone else's fingernail bed.

Finally, may I say that the original use for the sedimentation rate of Linzenmeier was in gynecology. Today, I think it is generally agreed that in practice and not necessarily in precise physiologic and biochemical laboratory, the best outfit for the study of the sedimentation rate is the Landau-Adams microsedimentation technique which is exceedingly simple and quite accurate, even when compared to the Westergren method.

DR. ODELL (Closing).—Our interest in the phenomena of "sludged blood" stems from the possibility that it might explain certain functional disturbances in pregnant patients, particularly in toxemias of pregnancy. The occurrence of edema and proteinuria in toxemia patients has never been well understood. And the circulation of clumped erythrocytes through the vascular system might interfere with normal metabolic exchange. We have noted particularly large intravascular agglutinations, and markedly elevated sedimentation rates in those toxemia patients with a pronounced proteinuria.

VITAMIN B COMPLEX, MENORRHAGIA, AND CANCER

A Critical Review*

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AN INCREASING number of publications have been concerned with the relation of vitamins of the B complex to the metabolism of estrogens in the human being. Deficiency of these vitamins has been assumed to be the indirect cause of various gynecologic disorders. Therapy with vitamin B complex is claimed to have cured these conditions.[3, 11-13] Insufficient vitamin B complex has also been implicated as a causal factor in the production of uterine carcinoma. This implication naturally has led to the suggestion that vitamins of the B complex might act as a prophylactic against the development of cancer.[3] A summary of the original article on vitamin B and carcinogenesis appeared in the editorial section of the *Journal of the American Medical Association*.[15] Widespread publicity resulted when it was discussed in some detail in two issues of a pharmaceutical firm publication sent to every physician.[1, 2]

Theories on the relation of B complex vitamins to gynecologic disorders and carcinogenesis have been based on an assumption which has recently been proved to be erroneous.[14] For this reason the present authors believe that a critical review of this subject would be of some value.

The hypothesis that vitamin B complex is related to gynecologic disorders and to carcinoma of the uterus may be stated as follows: The liver normally destroys or inactivates the estrogens produced in the body (endogenous estrogens). With insufficient vitamin B complex intake, the liver no longer has this ability or function. An excessive amount of estrogen results, which in turn is the cause of menorrhagia, metrorrhagia, premenstrual tension, and cystic mastitis.[11-13] Acting over long periods of time, the excessive estrogen may also induce uterine cancer.[3]

It is well established that the liver normally inactivates circulating estrogens or at least changes them to a much less active form. For example, Golden and Sevringhaus[22] found that the ovary transplanted to the mesentery of the experimental animal lived and flourished, as did the ovary transplanted to a subcutaneous site. The vagina of these latter animals showed estrogen stimulation. With the mesenteric graft, however, the vagina remained in a constant castrate condition. The venous drainage of the mesentery is directly to the liver via the portal vein. It is believed, therefore, that the liver inactivates the ovarian estrogen before it can reach the general circulation. Several workers have subsequently demonstrated that estrogens implanted as pellets[6, 7, 29, 30] or injected in solution into the spleen[36-38, 40] are also inactivated. The venous drainage here also is to the liver. The inactivation was not due to the spleen per se, since the subcutaneously transplanted spleen with a new blood supply draining into the systemic circulation had no inactivating effect. Other in vivo[35, 41, 47] and in vitro[17, 24, 25, 28, 34] experiments have also shown that the liver is able to inactivate estrogens.

There is some evidence in the human being that the liver inactivates estrogens.[4, 5, 16, 20, 21, 32, 48] For example, in cirrhosis of the liver in the male, there may be increased excretion of free estrogens in the urine and an associated gynecomastia.[21]

*Presented before the Chicago Gynecological Society, Dec. 20, 1946.

The hypothesis that vitamin B complex deficiency prevents the liver from inactivating estrogens is based on experimental work by M. S. and G. R. Biskind.[8, 9] Castrate animals with pellets of estrogen implanted into the spleen showed no estrogenic stimulation of the vaginal mucosa. After a period on a vitamin B complex free diet, however, the animals lost weight and the liver lost its ability to inactivate estrogens, since their vaginas showed constant estrogenic stimulation. Similar results were obtained by Shipley and Gyorgy.[42] Supportive data were furnished by Segaloff and Segaloff,[39] and others.[43] M. S. Biskind and Shelesnyak[10] have also reported that under similar conditions of vitamin B deprivation, the liver was unable to inactivate endogenous estrogen from ovarian tissue resident in the spleen.

In 1943 M. S. Biskind[11] claimed that the hypothesis also applied to the human being.

> "Evidence is presented that menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension, and possibly other syndromes related to an excess of estrogen are caused by a failure of the liver to inactivate estrogen because of deficiency of the vitamin B complex. Administration of the B complex in adequate dosage orally, parenterally, or by both routes, led to prompt improvement in these conditions."

This quotation represents the summary in toto from this article.

The evidence for these statements was derived from twenty-nine patients, of whom seven were discussed in detail. Atrophic glossitis, cheilosis, stomatitis, neuritic pains, or a combination of these symptoms was considered the evidence of vitamin B complex deficiency. The height and weight were noted in four of the seven cases, the average being only 5 feet, 2½ inches in height, but 160.25 pounds in weight. In the discussion the author states that most of the twenty-nine patients were overweight. Two of the early symptoms of the vitamin B complex deficiency are anorexia and loss of weight.[19, 44, 45] It is, therefore, unlikely that the obese patients at least were actually deficient.

The state of the endometrium was mentioned in only one patient. The tissue was obtained by curettage and showed hyperplasia of the endometrium. No other evidence was presented that the menorrhagia or metrorrhagia in the patients was actually caused by an excess of estrogen. The assumption that menorrhagia or metrorrhagia is in all cases due to an excess of estrogens is not valid. Such an excess would produce a hyperplasia of the endometrium and thus be easily demonstrable. Various workers have demonstrated that functional bleeding may be associated with endometrial hyperplasia. However, it may also be associated with merely a secretory type of endometrium or even atrophic endometrium. Hoffman studied the endometrium from 128 patients with functional bleeding, 20 to 35 years of age.[27] He found hyperplasia of the endometrium in 51 per cent, secretory type in 38 per cent, atrophic in 5 per cent, and early proliferative in 6 per cent. Sturgis Abarbanel, and Nader[46] found hyperplasia of the endometrium in only 35 per cent of a group of seventeen patients with menometrorrhagia. Hamblen,[23] in a series of 301 patients of all ages with menorrhagia, found "hyperestrogenic" endometrium in 25.6 per cent. This group contained many adolescent and climacteric women. In a group of 129 which included few adolescent or climacteric women, hyperestrogenic endometrium was found in only 11.8 per cent. The figures presented here do not include the endometria classified by Hamblen as "persistent estrogenic." These showed "no active proliferation but instead cytologic and functional evidences of regression." These are not the findings that would be obtained with an excess of estrogen.

In 1944 a second paper on this subject was published jointly by the three Biskinds.[12] The series was "extended to include studies on 104 patients of

whom seventy were treated with various preparations of vitamin B complex." According to these authors "the response to vitamin B complex therapy in these patients was usually prompt and often dramatic. Some of the patients showed only moderate improvement on oral therapy; as impairment of absorption and utilization occurs frequently in nutritional deficiency, these patients were given parenteral therapy in addition. With the latter, striking improvement, especially in premenstrual tension and in painful breasts, often occurred in as little as a few hours to at most a day or two."

Details were given on four patients, and more or less brief data were presented in tabular form on 43 more patients. With the exception of one 212-pound patient, body weight was not mentioned. No specific data were given as to the status of the endometrium, although it was stated that "studies on the endometriums of the cases with pathologic uterine bleeding are still under way."

In addition to the benefits in gynecologic disorders, the authors also credit the B complex therapy with other equally desirable effects. These include improvement of psoriasis, healing of intertrigo, clearing of acne, induction of the ability to tan rather than just sunborn, redistribution of fat so that while there was no weight loss, the circumference of excessively developed hips and breasts was reduced; disappearance of a mass from the breast that had been present for a decade, diminution in size (but not complete regression) of enlarged thyroids, and a clearing and brightening of the complexion.

Later in 1944 L. M. and M. S. Biskind[13] reported an "accelerated postpartum involution of the uterus with vitamin B complex." One hundred seven control patients were judged to be consuming an adequate diet and were given no supplementary vitamins. Seventy-six treated patients were given B complex "solely for nutritional reasons when it became apparent that the average diet in pregnancy needed supplementation." Treatment was given only during pregnancy and not in the postpartum period. The degree or extent of postpartum involution at six weeks post partum was determined by bimanual examination.

This work was based "on the assumption that postpartum uterine subinvolution is related to excess estrogen, and that this excess is due to failure of destruction in the liver owing to deficiencies of the factors of the vitamin B complex." No evidence was presented that estrogen actually does or can cause subinvolution of the uterus. To our knowledge no such evidence exists.

In April, 1946, vitamin B complex deficiency (specifically thiamine and riboflavin) was implicated as a cause of cancer of the uterus as well as menorrhagia by Ayre and Bauld.[3] Their observations included the findings in 150 patients with carcinoma of the uterus. According to these authors the "vaginal and cervical cytology smear" showed evidence of abnormally high endogenous estrogenic activity in two-thirds of the patients with uterine cancer.

Ayre and Bauld quoted extensively from the works of the Biskinds and, like them, believe that the cause of the excess endogenous estrogen (which caused the menorrhagia or the cancer) was an insufficiency of one or more of the vitamins of the B complex in the diet. This deficiency prevented the liver from carrying out its normal function of destroying or inactivating estrogen.

Detailed data were presented on three patients. All three "were bleeding excessively, and all showed abnormally high estrogen level in the cytology smears as well as thiamine deficiency" as judged by their response to a "vitamin-tolerance technique." The first of these patients, who was 29 years old, had either a "squamous intra-epithelial carcinoma" of the cervix or a "precancerous secondary hyperplasia" of the cervix. The second was 14 years of age and her endometrium showed "overstimulated proliferative glands with mitosis and adenomatous formation such as would make the pathologist think

twice before eliminating a diagnosis of precancerous change if found in a 40-year-old." The third patient was 64 years old and had a typical squamous cell carcinoma of the cervix.

As an addendum to their paper Ayre and Bauld state that of twenty patients suffering from uterine cancer, 90 per cent had a low thiamine excretion coupled with abnormally high endogenous estrogen level, and 20 per cent also showed a deficient excretion of riboflavin. The authors conclude that if their work were confirmed and their theories substantiated, one could detect a potential cancer-producing mechanism even before the cancer develops. A combination of low thiamin and abnormally high endogenous estrogen could be recognized as a dangerous precancerous condition. Recognition of the findings and their dietetic correction would thus prevent the development of cancer.

Ayre and Bauld used the "vaginal and cervical cytological smear" as a quantitative index of endogenous estrogen production. The validity of using this particular method to determine that excessive endogenous estrogens are being produced in a patient has yet to be established. The smear is valuable in differentiating whether the vaginal mucosa is or is not stimulated by estrogens. It may even be considered quantitative in that one can distinguish between a full estrogenic effect (due to optimal amounts of endogenous or administered estrogens) and a partial effect due to less than optimal amounts. The vaginal mucosa (and that of the portio portion of the cervix) responds as much as it is able to optimal amounts of estrogen. This maximal growth response is reflected in the desquamated cells found in the smear. Since the vaginal mucosa is already responding to the greatest of its ability under optimal conditions, there can be no further response to excessive amounts of estrogen. Ayre and Bauld made only the statement that the presence of excessive amounts of estrogens was determined by the "vaginal and cervical cytology smear." No mention was made of their findings in the smear that indicates this excessive estrogen. They did not quote any data of their own or publications of other workers to establish the validity of this method.

Ayre and Bauld attach great significance to the finding of cornified smears from a vaginal mucosa of the functional type in postmenopausal women with uterine cancer. However, McLaren[31] has demonstrated both by smear and by biopsy that functional type cornified vaginal mucosa may be found in at least 65 per cent of normal postmenopausal women. This figure seems high, but Salmon and Frank[33] found vaginal smears of the functional or estrogenic type consistently in 30 per cent of postmenopausal women, and intermittently with repeated smearing in another 30 per cent of postmenopausal women. In only 40 per cent were the smears consistently negative. Ayre and Bauld's findings are, therefore, of dubious significance, unless it can be demonstrated that such smears are significantly more frequent in the postmenopausal women with cancer than in postmenopausal women without cancer.

Other workers have stressed the findings of proliferative endometrium or endometrial hyperplasia with carcinoma of the uterus. This has also been used as evidence that excess endogenous estrogen causes the carcinoma. However, Fahlund and Broders[18] compared the endometrium from postmenopausal women with adenocarcinoma of the corpus uteri to those without carcinoma. In their series they found "no appreciable difference in the percentage of cases of any given type of endometrium in adenocarcinomatous uteri as compared with non-adenocarcinomatous uteri, except with regard to atrophic endometrium." Atrophic endometrium (little or no estrogenic stimulation) was found *more frequently* in the carcinomatous than in the noncarcinomatous uterus.

The editorial in the *Journal of the American Medical Association* was limited to a summary of the original article by Ayre and Bauld. There was no critical evaluation of the literature on the subject.

Attention was drawn to the chemical "similarity" of estrogens and some of the true chemical carcinogens. This "similarity" has been commented on in many articles in the past. It consists of the presence of the phenanthrene nucleus as a part of the molecule in both estrogens and carcinogens. The implication, of course, is that the chemical similarity endows the estrogen with carcinogenic properties. The implication is not logical since androgens, progesterone, bile acids, cholesterol, and even vitamin D have this same phenanthrene nucleus as part of their molecular structure.

The editorial quotes an article by Henry[26]—as did Ayre and Bauld—which reports "two cases in which the prolonged administration of diethylstilbestrol has been followed by the discovery of malignant growths in the uterus." Read-in the original article reveals the fact that in neither of these patients could the many pathologists examining the tissues agree whether the tumors were malignant or not. Such findings are equivocal.

The rationale for treatment, the explanation for the unusually uniform and rather remarkable therapeutic response of the Biskinds' patients, as well as the theory behind the work of Ayre and Bauld, are necessarily based on the major assumption that vitamin B complex deficiency per se renders the liver incapable of inactivating estrogens.

Recently Drill and Pfeiffer[14] have conclusively proved that the vitamin B complex deficiency was not the factor that made the liver unable to inactivate estrogen in the experimental animal, but that the real cause was the associated caloric deficiency. Every worker in this field has long been aware that the experimental animal on a B complex deficient diet refused to eat more than a very little, rapidly becomes emaciated, and eventually dies of self-induced starvation. Vital functions are, of course, at a minimum during starvation or even semistarvation. Drill wished to determine whether the inability of the liver to inactivate estrogens was due to the vitamin deficiency or due to the markedly reduced caloric intake. Accordingly, his control animals on a diet qualitatively normal were given each day exactly the same amount of food that the animals on the B complex deficient diet had eaten the day before. After approximately the same period of time the livers of *both* groups of animals lost their ability to inactivate the estrogen absorbed from the pellets implanted in their spleens. He demonstrated further that the phenomenon was due to inanition because of an inadequate caloric intake. Animals were given a calorically restricted diet and force fed with a more than adequate amount of the various vitamin B factors. In spite of all the added B vitamins, the livers of these animals also were unable to inactivate the estrogen.

Summary

This critical review of the literature is concerned with the function of the liver in the inactivation of estrogens; the effect of vitamin B complex deficiency on this function; the relation of vitamin B complex deficiency to various gynecologic disorders and to cancer of the uterus; and the therapeutic use of this substance in these conditions.

The clinical work is founded on the basic assumption that vitamin B complex deficiency renders the liver unable to inactivate estrogens. This leads to the accumulation of excessive endogenous estrogens which in turn cause the menorrhagia or may after prolonged action cause carcinoma of the uterus. The validity of the theory is evidently destroyed.

Anorexia and weight loss are early symptoms of vitamin B complex deficiency. The subjects of these articles were not reported as having had such symptoms. In fact, in one article it was specifically stated that most of the patients were overweight. It seems doubtful that these patients, at least, actually were deficient.

It is postulated in these clinical articles that excessive endogenous estrogens result from the inability of the vitamin deficient liver to inactivate them. In the Biskinds' articles no specific evidence has been presented that excessive estrogens actually are present. Ayre and Bauld state that evidence of the presence of excessive endogenous estrogens was in their vaginal and cervical cytology smears, yet they do not present evidence to substantiate this claim. The known physiology of the vagina makes it unlikely.

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Discussion

DR. JOHN W. HUFFMAN.—I would welcome the conviction that a deficiency of vitamin B-complex causes most of the common gynecologic complaints and that they could

be relieved by its administration. To establish this conviction the proponents of the vitamin B complex deficiency theory ask us to accept certain reasoning, to wit: that the diets of a large group of women suffering from varied gynecologic disorders are seriously depleted of vitamin B complex; that the liver, due to this B-complex deficiency, fails to destroy estrogens; that a high estrogen level results because of this liver malfunction; that this estrogen level becomes high and remains high enough to produce menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension, leucorrhea, uterine fibromyomas, fat pads about the hips, acne, muddy complexion, and carcinoma of the uterus; only this week dysmenorrhea was added to the list (all that remains to be added are threatened and habitual abortion). If we entertain this reasoning we may then, I think, properly ask the proponents of these hypotheses to show us by analysis of the diets of their patients that these diets were actually deficient in vitamin B complex. This they have not done. If we entertain this reasoning then we may expect its proponents to show us that these patients are actually deficient in vitamin B complex. This can be accomplished with a moderate degree of accuracy by a vitamin tolerance test. This was done in only a small group of patients. If we accept this reasoning we may expect its proponents to show us that the women they treated did have a high estrogen level as established by blood estrogen levels, even by estrogen excretion determinations. This they have not done. Last, we might properly expect these proponents to demonstrate to us that the many problems they attribute to a vitamin B complex deficiency actually are due to hyperestrogenism. I believe that many thoughtful clinical investigators are still unconvinced that hyperestrogenism is the principal cause for many of these ills. In addition, we might properly ask them to show us that women who suffer from these complaints and who do not exhibit clinical evidence of B-complex deficiency will be specifically benefited by its administration. There can be little doubt that individuals suffering from severe avitaminosis will have an impairment in their general health and that the genitals will participate in the derangements which are a part of that ill-health. Furthermore it is a common observation that vitamin-B complex does give a general sense of well-being and is of benefit in so-called "run-down" and under-par individuals. This is a far cry, however, from assigning to it, on the basis of present knowledge at least, a specific role in the causation and treatment of the many ills we have heard mentioned.

Again, I wish to say that I welcome the conviction that vitamin B complex will do the things that the proponents of this interesting hypothesis we have heard described claim for it. It will indeed be a relief to feel certain that I can forestall malignancy by its use and that I can treat the majority of the patients who come to me with one common panacea.

PREGNANCY ASSOCIATED WITH DIABETES*

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FROM Jan. 1, 1933, to Dec. 31, 1946, inclusive, 9,273 obstetric deliveries were made at the Mayo Clinic. The annual number of deliveries ranged from 384 in 1933 to 1,218 in 1946. In this period of fourteen years, we observed forty pregnant women who had diabetes. The forty diabetic women gave birth to fifty infants. No instance of multiple pregnancy was observed in these cases. Cesarean section was performed twenty-six times on twenty-two of the women. One of the infants delivered in this manner died in the neonatal period. Vaginal delivery was performed twenty-four times on nineteen of the women.† Of the twenty-four infants who were delivered through the vagina, fifteen survived, six were stillborn, and three died in the neonatal period. The fetal survival rate was 96.2 per cent in the instances in which cesarean section was performed, and 62.5 per cent in the instances in which the delivery was made through the vagina. All of the mothers survived. The clinical data in the two groups of cases are shown in Tables I and II.

In seven of the twenty-two cases in which cesarean section was performed, the patients previously had given birth to a dead fetus. In one of the seven cases, a stillbirth had occurred on two occasions. In four of the twenty-two cases, there was a history of neonatal death. One patient previously had been infertile, and dystocia previously had necessitated a difficult forceps delivery in one case. In three of the twenty-two cases in this group, the diabetes was difficult to control, and accident to the child was feared. Toxemia was present in eight cases. In one of the eight cases, toxemia occurred in two pregnancies in which the patient was observed at the clinic. Although the toxemia responded to treatment in some cases, it still was considered an added risk to the fetus. In five of the twenty-two cases in which cesarean section was performed, diabetes was the only complication. In several cases there was more than one indication for cesarean section.

We were able to select the method of delivery in thirty-one, or 62 per cent, of the fifty instances, that is, in all of the twenty-six instances in which cesarean section was performed and in five of the twenty-four instances in which vaginal delivery was employed. In two of the five instances in which vaginal delivery was selected, spontaneous labor occurred at or near term; in three instances, labor was induced. In six of the remaining nineteen instances in which vaginal delivery was employed, the fetus was dead. In thirteen instances, labor commenced prematurely and spontaneously while the fetus was alive.

The loss of nine of the twenty-four infants delivered through the vagina merits brief comment. In four instances the mother cooperated poorly in the care of the diabetes and severe acidosis no doubt contributed to the fetal mortality. The patient who had eclampsia came to the clinic for emergency treatment after the fetus had died in utero. In the case in which premature

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†One of the forty patients was observed in four pregnancies. Cesarean section was performed once and vaginal delivery was employed on three occasions.

separation of the placenta occurred, the diabetes was controlled satisfactorily and there was no evidence of toxemia. In one case, acidosis was present and no fetal heart sounds could be heard when the patient was admitted to the hospital. In two cases in which the diabetes was controlled satisfactorily and other complications were not present, the fetuses died in utero at the thirty-sixth and thirty-seventh weeks of pregnancy, respectively.

In 1936, Rynearson and I reported seven consecutive cases in which diabetic women were delivered of infants. Cesarean section was performed in six of the seven cases; in the remaining case, the infant was delivered through the vagina. Cesarean section was the treatment of choice at the time these patients were observed. We emphasized that hypoglycemia of the newborn infant was a frequent cause of neonatal morbidity and mortality, and we recommended that cesarean section at about the thirty-sixth week of gestation should be seriously considered for the delivery of the over-mature and overweight fetus of a diabetic woman. We advised watching for the development of hypoglycemia in the infant and stressed the importance of correcting this condition.

In the past ten years a considerable number of cases of diabetes and coexisting pregnancy have been reported. Until recently, the infant mortality and morbidity have not always been satisfactory, although the maternal risk has been minimal in cases in which adequate cooperation has existed between the patients and their physicians. A satisfactory explanation has not been found for the previously high incidence of infant mortality and morbidity. Perhaps the excellent work of Smith, Smith, and Hurwitz and of White will not serve to avoid all of the accidents to infants of diabetic mothers, for disturbances of metabolism incident to a combination of diabetes and pregnancy are necessarily complex. However, the results of correction of the imbalance between amounts of chorionic prolan and placental steroids resulted in a fetal salvage of 90 per cent, and White further reported a fetal survival rate of 96 per cent in cases in which diabetic mothers had a normal hormonal balance.

My experience with this concept of correction of hormonal imbalance is limited to eight cases. In six of these cases, the infants survived. Cesarean section was performed in two of these cases, and both of the infants lived. Toxemia was present in both of the cases and the diabetes was severe ("brittle") in one of the cases. In two cases, labor was induced at the thirty-fifth and thirty-eighth weeks of pregnancy, respectively, and live infants were delivered.

In four cases, labor commenced prematurely and delivery was made through the vagina. Premature separation of the placenta occurred in one of these cases. In this case, the child was stillborn. In one case, in which labor occurred at the thirtieth week of pregnancy, after coma and acidosis in the mother, the infant died in the neonatal period. In the two remaining cases, the infants lived. In one of these cases, the infant weighed 4,080 Gm. when born at the thirty-sixth week of gestation. In the other case, the infant weighed 4,210 Gm. and was delivered by a difficult forceps procedure.

It is to be hoped that recognition and correction of the hormonal imbalance, when present in diabetic women who are pregnant, will result in a higher

TABLE I. DATA IN TWENTY-TWO CASES IN WHICH CESAREAN SECTION WAS PERFORMED

CASE	AGE (YR.)	GRAVIDA	PARA	WEEKS OF GESTATION	INFANT WEIGHT (GM.)	INFANT FATE	COMMENT
1	29	ii	i	36	3,660	Lived	Diabetes, grade 4, at 28 years; stillbirth at 26 years
2	26	iii	ii	34	2,960	Lived	Diabetes, grade 3, at 23 years; premature living infant as gravida i; stillbirth following diabetic coma as gravida ii
3	33	ii	i	36	3,290	Lived	Diabetes, grade 3, at 27 years; neonatal death of premature infant as gravida i; subsequent vaginal delivery of two premature infants, 2,520 Gm. (33 wk.) and 1,980 Gm. (31 wk.) respectively, both of whom survived
4	22	i	0	36	3,310	Lived	Diabetes, grade 4, at 20 years; severe (''brittle'') diabetes; elective cesarean section
5	41	v	iii	36	3,240	Lived	Diabetes, grade 3, at first pregnancy at 34 years; patient uncooperative; first seen in severe acidosis in twenty-ninth week of pregnancy
6	28	ii	i	37	2,970	Lived	Diabetes, grade 3, at 25 years; first child stillborn
7	30	i	0	33	1,900	Lived	Diabetes, grade 3, at 26 years; patient first seen in severe toxemia which did not respond to treatment
8	29	iii	ii	38	3,560	Lived	Diabetes, grade 4, at 22 years; toxemia; ligation of tubes
9	24	ii	i	36	3,670	Lived	Diabetes, grade 3, in seventh month of first pregnancy at 22 years; stillbirth following acidosis
	26	iii	ii	35	3,830	Lived	Sterilization
10	29	ii	i	36	2,870	Lived	Diabetes, grade 3; mild toxemia; neonatal death of first child
11	26	i	0	36	3,624	Lived	Diabetes, grade 4, at 13 years; toxemia; severe retinitis
	27	ii	i	35	3,138	Lived	Toxemia
12	24	i	0	36	3,240	Lived	Diabetes, grade 3, at 17 years; toxemia which responded only partially to treatment
13*	27	iii	ii	33	3,120	Lived	Diabetes, grade 4, at 16 years; neonatal death of first child; second child stillborn; subsequent vaginal delivery of premature infant that lived
14	39	ii	i	36	2,760	Lived	Diabetes, grade 4, at 24 years; premature stillbirth at 34 years; toxemia; ligation of tubes
15	28	ii	i	38	3,360	Lived	Diabetes, grade 4, at first pregnancy at 25 years; first child delivered alive with forceps; ligation of tubes
16	23	i	0	36	2,780	Lived	Diabetes discovered in pregnancy; elective cesarean section
17	19	i	0	37	3,450	Lived	Diabetes, grade 4, at 15 years; severe (''brittle'') diabetes; coma once and severe acidosis once during pregnancy; toxemia which did not respond to treatment; subsequent premature delivery with neonatal death following diabetic coma 3 weeks previously and acidosis on admission to hospital

TABLE I.—CONT'D

CASE	AGE (YR.)	GRAV-IDA	PARA	WEEKS OF GES-TATION	INFANT WEIGHT (GM.)	INFANT FATE	COMMENT
18	27	i	0	37	2,460	Lived	Diabetes, grade 4, at 16 years; severe (''brittle'') diabetes; toxemia
19	36	v	iv	37	3,402	Lived	Diabetes, grade 3, at 30 years; first pregnancy terminated at sixth month; second pregnancy terminated at eighth month; third pregnancy terminated at seventh month (live child); fourth pregnancy terminated at seventh month (neonatal death)
20	29	i	0	37	3,175	Lived	Diabetes at 24 years; elective cesarean section
21	23	iii	i	36	3,040	Lived	Diabetes at 19 years; two previous stillbirths; elective cesarean section
22	32	i	0	37	3,941	Lived	Diabetes, grade 4, at 28 years; previous infertility
	36	ii	i	36	3,624	Lived	Elective cesarean section
	38	iii	ii	35	3,804	Neonatal death	Elective cesarean section; ligation of tubes

*This is the same case as Case 12 in Table II. Although the cases in this table and Table II total forty-one, there were only forty diabetic patients.

percentage of normal deliveries. As is true in all obstetric conditions, a careful study of all factors involved in a given case should lead to proper selection of treatment. There is and will continue to be a difference of opinion in regard to the delivery of diabetic women.

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Discussion

DR. M. DAVID ALLWEISS.—We can certainly say that there is agreement in the literature that the pregnant diabetic must be controlled and well regulated. This is not a big problem in the cooperative patient where the use of protamine insulin with a fuller diet and small doses of regular insulin have made this problem minor.

The second problem is that of the newborn infant. This has interested us and we have found that hypoglycemia occurs within the first fifty minutes after birth. This is corrected with glucose given to the infant by mouth.

The third problem is the one presented by White in hormone imbalance. We have followed the literature carefully on this but we have had no experience with it. We have not had the toxemia others have reported.

The fourth problem is that of delivery. As an internist, we can give this problem back to the obstetrician. Dr. Randall infers that he believes in cesarean section. We believe in it, too, because out of 39 patients 36 have been sectioned with no infant mortality. Of the three delivering from below, two infants died.

One of the most important things I got out of Dr. Randall's paper is this: If the infant is small and if labor could be induced at about thirty-six weeks and the patient be delivered from below, a live baby would be the result. Several of his patients went into spontaneous labor around the thirty-sixth week and still the baby died. We do not know the answer for this. Perhaps it is the large, bulky baby being pulled through the vaginal

TABLE II. DATA IN NINETEEN CASES IN WHICH VAGINAL DELIVERY WAS EMPLOYED

CASE	AGE YEARS	GRAVIDA	PARA	LABOR	PREMATURE RUPTURE OF MEMBRANES	WEEKS OF GESTATION	INFANT		COMMENT
							WEIGHT (GM.)	FATE	
1	41	xiii	ix	Spontaneous	+	36	4,080	Lived	Diabetes, grade 4, at 40 years; mother Rh negative
2	35	iii	ii	Spontaneous	+	33	2,520	Lived	Diabetes, grade 3, at 27 years; cesarean section as gravida ii, at 33 years, because of neonatal death of first child; acidosis when patient was admitted to hospital
	38	iv	iii	Spontaneous	0	31	1,980	Lived	Hydramnios; retinitis
3	31	i	0	Spontaneous	+	33	3,460	Lived	Diabetes, grade 4, at 29 years; mild toxemia; outlet forceps
4	36	v	iii	Spontaneous	+	36	3,640	Lived	Diabetes, grade 4, at 34 years
5	21	i	0	Induced	0	35	2,630	Lived	Diabetes, grade 4, at 14 years; marked hydramnios; diabetic retinitis; albuminuria, grade 3; edema, grade 2
6	32	viii	vi	Spontaneous	0	36	3,620	Lived	Diabetes discovered in this pregnancy
7	31	iii	ii	Induced	+	38	3,360	Lived	Diabetes, grade 4, at 18 years; stillbirth at 21 years; second pregnancy (living child) at 24 years; retinitis
8	29	i	0	Induced	+	38	4,210	Lived	Diabetes at 12 years; toxemia; low forceps
9	31	iii	ii			40	3,216	Lived	Diabetes at 26 years
10	17	i	0	Spontaneous	+	36	3,460	Lived	Diabetes, grade 4, at 13 years; hypertension

11	31	v	iv	Spontaneous	0	37	2,964	Stillborn and macerated	Diabetes, grade 2
	37	viii	vii	Spontaneous		36	3,020	Mongolian idiot, lived	
12*	23	i	0	Spontaneous	+	26	1,540	Neonatal death	Diabetes, grade 4, at 16 years; hydramnios, grade 2; patient uncooperative
	24	ii	i	Spontaneous	+	34	2,860	Stillborn	Hydramnios, grade 2; patient admitted in acidosis
	29	iv	iii	Spontaneous	+	33	2,230	Lived	Hydramnios, grade 2
13	20	ii	0	Spontaneous	0	35	1,980	Neonatal death	Diabetes, grade 4, at 19 years; patient uncooperative
	24	iv	iii	Spontaneous	0	32	2,450	Lived	Infant had congenital cardiac defect
14	37	ii	i	Induced	+	36	3,460	Stillborn	Diabetes at 33 years; labor induced because of death of fetus
15	27	i	0	Induced	0	37		Stillborn	Diabetes, grade 3, at 23 years; patient admitted with eclampsia and dead fetus in uterus
16	22	i	0	Spontaneous	0	30		Neonatal death	Diabetes, grade 4, at 15 years; patient uncooperative
17	25	ii	0	Spontaneous	0	33	2,440	Stillborn	Diabetes at 14 years; toxemia; patient uncooperative
18	26	iii	ii			37	3,580	Stillborn	Premature separation of placenta
19	28	ii	i	Spontaneous	0	38	3,630	Lived	

*This is the same case as Case 13 in Table I. Although the cases in this table and Table I total forty-one, there were only forty diabetic patients.

canal and not strong enough to withstand the trauma as do normal babies delivered spontaneously. When the diabetic pregnant person presents herself to an obstetrician she wants a live baby, and apparently the way to get it is by cesarean section at about the thirty-sixth week, good care of the mother throughout pregnancy, and special care to the infant within the first fifty minutes after birth.

DR. CHESTER COGGESHALL.—I suspect that Dr. Randall presented this conservative paper on his experiences with pregnancy and diabetes for one very valid reason: that the cold facts presented here could bear more weight than anything else.

Both the treatment of diabetes and of pregnancy associated with diabetes are relatively new medical approaches dating from the discovery of insulin. Prior to insulin few women of the childbearing age with diabetes became pregnant. Many were nonovulatory and many had primary amenorrhea.

I am sure that Dr. Randall has not presented this paper with the purpose of offering cesarean section as the answer to the high fetal mortality rate in this condition, and obviously his second group of diabetics delivered vaginally bears this out. Cesarean section is not the answer to the high percentage of stillbirths.

I was fortunate in being associated with Dr. White when she began her very interesting work. The amount of adverse criticism was tremendous at that time both within our own group in Boston and throughout the country. Since that time I have found that the internist feels that Dr. White has contributed greatly in her study of abnormal hormonal balance in the diabetic pregnant woman. I called her last night because I know how keenly she feels about this subject and I am privileged to give you a brief, up-to-date report of her latest cases: of 336 diabetic pregnant women since January, 1936, 71 had normal hormonal balance as determined by her study; there were two deaths in that series, or a fetal survival rate of 97 per cent. Sixty-one patients showed abnormal hormonal balance as determined by her study, and were not treated but were used as controls; in that group she obtained 44 per cent fetal survival rate. Two hundred four abnormal hormonal balance cases were treated by the use of large doses of stilbesterol, and in this series Dr. White obtained a 90.5 per cent fetal survival rate.

Dr. Randall's paper and the statistics from any large pregnancy series concerned with diabetes will bear out that these are remarkable figures of Dr. White. They should be of great interest and should force upon the obstetrician a program of definite observation and treatment along medical lines and a program of research.

What should be your role in the pregnant diabetic? First of all I think it is important to establish whether it is a true diabetes or not. I think the management of the diabetes should be given over to an internist especially qualified in the subject. I think, as Dr. White does, that we should not rely upon the older signs of impending toxemia, such as edema, albuminuria, rising blood pressure, but that by thorough investigative work the excretion studies of pregnandiol should be made. Dr. White believes that a simple method of examining vaginal smears for the disappearance of basophilic cells may be of some help to the obstetrician who practices without a laboratory.

The most important consideration, as you see these diabetic women, is to realize what diabetes really means to that patient. I am grieved to have to state that, despite the admirable weapons we have for its treatment, the longer the patient with diabetes is kept alive, the more surely we see signs of degeneration, particularly arteriosclerosis. They are prematurely aged individuals. It may be the arteriosclerosis itself or it may be, as Dr. White suggested, secondary premature ovarian failure which accounts for the high amount of toxemia in these pregnant women. I think Dr. Randall's paper bears out the fact that the longer the diabetes has been present, the greater the chance of toxemia and the more necessary the choice of early delivery by cesarean section until we have learned more about the subject.

DR. EDWARD L. CORNELL.—I agree thoroughly with Dr. Coggeshall that these patients should be under the care of a man competent to control the diabetes. That is a primary factor in order to secure a live baby.

I have not used cesarean section routinely for the delivery of these patients. I have endeavored to select the cases. If they give a history of previous stillbirths or miscarriages, cesarean section is certainly advised as soon as the baby is viable. I usually have an x-ray taken to try to determine the size of the baby.

I want to caution that these babies should be watched carefully after delivery because they seem to be poor risks. Hypoglycemia and other problems arise so the obstetrician should be on the alert at all times in the management of these babies during the first ten days of life.

Toxemia in my experience has not been as frequent as it has in Dr. Randall's series. I see it occasionally.

I would like to ask Dr. Randall what method of induction of labor he employs in those patients delivered vaginally.

DR. RANDALL (Closing).—As I have said before, I am not too happy about our experiences in this condition. I think it can be improved. I think the points brought out by the discussants serve to emphasize that these patients are problems that we have to take care of in conjunction with the internist. I should pay particular tribute to the pediatric staff who watched these babies carefully after they were born.

As to the method of induction of labor, mostly we have ruptured the membranes. We have, however, been extremely loath to induce labor in this manner in a primigravid woman of thirty-five to thirty-six weeks. Too frequently under these circumstances the cervix is uneffaced and the resulting labor is likely to be increased in length, and I doubt that the infant of a diabetic mother should be subjected to a prolonged labor. It seems to me that cesarean section is better treatment.

THE TREATMENT OF CARCINOMA OF THE VULVA*

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THERE is still considerable confusion as to the effectiveness of the various forms of therapy which are being advocated and used for vulvar carcinoma. This is apparently due to the fact that the disease is comparatively rare, and few investigators have had sufficient experience with it to justify dogmatic conclusions. Many have not hesitated to express unproved opinions, but one can only be surprised on reading the literature to realize how little factual support there is for such opinions. The outstanding exception is the work of Taussig. In spite of this, two rather disturbing facts must be faced. Papers are appearing which advocate extensive surgical procedures without any statement as to their applicability or results. Second, one cannot escape the fact that a large proportion of patients with this disease are in actual practice being handled by demonstrably ineffective measures which effectively preclude a reasonable chance of subsequent cure.

Those who have to deal with the problem must decide on some form of attack. It is the object of this paper to attempt to evaluate the results of such a decision at the University of Minnesota Medical School, to compare the results of the presently used radical vulvectomy with other types of procedures previously used, and to present what information has come from the material in regard to the further extension of the surgical attack.

The material represents all of the vulvar carcinomas seen from 1928 to the end of 1946 and is shown in Table I. It falls into two groups. Prior to September, 1938, the thirty-six patients were treated by a wide variety of measures including simple vulvectomy, unilateral and bilateral superficial, and both superficial and deep gland removal, x-ray to groin, and/or to vulva, and radium or radon application to vulva or groin. These were done at various time intervals and in various combinations so that there were nearly half as many types of procedures used as there were patients. This sort of extensive individualization of therapy had certain advantages, but can now be tested for curative results. No single stage radical vulvectomy was used. This material has been described in more detail elsewhere.[7]

In September, 1938, an attempt to standardize therapy was introduced. The radical vulvectomy to be described was used and its applicability to the group is shown in the table.

The radical vulvectomy which was used has not varied significantly except as necessary to handle the variations of extension of the tumor to urethra, vagina, or perirectal glands. Occasionally in the more extensive tumors, radon

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seeds have been applied at operation to the margin of the incision closest to the tumor to deliver 7 erythema skin doses (7,000 gamma roentgens) to an area 1 cm. wide. Local 0.5 per cent procaine, with or without adrenalin 1-1,000, up to 3 drops per 30 c.c. of solution depending upon the usual criteria for this, was used on all. Preparation for this involves the exhibition of 6 grains of sodium amytal three hours before operation. The patient is seen one and one-half hours later when a further 3 grains of sodium amytal may or may not be added depending on age, size, and response. Hyoscine in doses of $\frac{1}{150}$ or $\frac{1}{200}$ is given at this time. Demerol or morphia may occasionally be added during the operation. The finer details of the infiltration technique need not concern us here. Strict precautions are taken to avoid infiltrating tumor-bearing tissue. It is necessary to reinfiltrate the femoral and inguinal canal regions and that of the clitoris as these are approached. A wide mass of lymphatic-bearing fat is dissected out from what is usually an approximation of the superficial lamella down to the fascia lata, the external oblique muscle, and the periosteum of the symphysis, and this is left attached medially. The inguinal canal is usually opened, but under any circumstances is cleaned of its lymphatic-bearing fat to the peritoneum. The upper 5-6 cm. of the saphenous vein is removed. The cribriform fascia is removed, and the femoral canal cleaned of its lymphatic tissue to the peritoneum. Hernial closures are done on both femoral and inguinal canals. An operator and assistant on each side allows this dissection to be done on the two sides simultaneously. Various amounts of skin are removed and closure done. The vulva is then infiltrated with procaine solution, and a wide excision is carried out removing all of the subcutaneous fat and as much of the vulvar skin and vagina as possible. Leucoplakic skin about the anus is also removed, but the anus is not circumcised when tumor does not involve this area. One can better avoid anal strictures by removing the remainder of the leucoplakia at a second sitting after healing of the partial excision. The whole mass is thus removed in one piece. The vulva area is closed as completely as possible. A retention catheter is placed and the wound dressed with sea sponges and elastic tape for pressure. The patients are allowed out of bed and walk on the day of operation and each day thereafter. Many of the wounds break down and secondary closures or pinch grafting is done later as indicated.

A word might be said here as to the use of local anesthesia. It requires a good deal from the operator. He must obtain the confidence of his patient. There is little skill required for its application but it prolongs the operation and requires gentleness and patience. What discomfort there is for the patient seems to be more than offset by its safety. It alone has allowed wide applicability of curative surgical attempts to many of these patients. Their ages ranged from 36 to 84 years, with three over 80 years and eleven between 70 and 80 years. No patient was excluded from operation because of general physical disability. Of the six who were not treated by radical vulvectomy, three had hopeless tumors for even palliation, one refused treatment, one was treated as a carcinoma of the vagina, and one had a microscopic tumor. The earliest postoperative death was on the sixteenth postoperative day. No death had any direct relationship to the surgical procedure itself or to the anesthesia. About two-thirds of the patients have no or very little memory of the operative day. In our hands it has given satisfactory pain relief.

There were 36 patients seen prior to September, 1938 (Table I). Four were not treated, all because of hopelessly extensive tumors. That these were well excluded is shown by the fact that three died in less than a month and one in ten months, all of carcinoma. The general nature of the treatment of the remaining 32 patients was indicated above, but none were treated by radical vulvectomy. There were only two deaths in the postoperative period for

TABLE I. CARCINOMA OF THE VULVA, 1928 TO 1946

Total	80			
To Sept., 1938	36			
Not treated		4	4	Died of carcinoma
Treated (no radical vulvectomy)		32	26	Died 2 postoperative emboli
				Died 1 vascular disease—19 months; no tumor
				Died 23 carcinoma
			5	Alive and cured 5 years or more
			1	Alive with tumor—150 months
Sept., 1938-1946	44			
Not treated		4	3	Died of carcinoma
			1	Alive with tumor 62 months
Treated (radical vulvectomy)		38	15	Died 1 postoperative embolus
				Died 1 postoperative pyelonephritis
				Died 1 heart block pre- and postoperative
				Died 1 ? cause, postoperative
				Died 3 apoplexy at 2, 4, and 59 months; no tumor
				Died 1 accidental at 40 months; no tumor
				Died 7 carcinoma
			4	Alive and cured 5 years or more
			18	Alive, no tumor, 2 to 59 months
			1	Alive with tumor, 46 months
Treated (other than radical vulvectomy)		1	1	Alive and cured 70 months (microscopic tumor simple vulvectomy)
		1	1	Alive with tumor, 41 months (probably carcinoma of vagina)

a mortality rate of 6 per cent. Both of these followed simple vulvectomy. Of the remaining 24 who died, 23 died of carcinoma of the vulva. This is surprising, since one would expect considerably greater interference with the cure rate from deaths due to noncarcinomatous causes in a disease of such relatively advanced age as this. Five are alive and free of tumor five years or more after treatment for an absolute cure rate of 13.9 per cent or a relative cure rate of 15.6 per cent. These five patients have been alive and free of tumor from 101 to 222 months. Four had simple vulvectomies and x-ray to the groin. One of these had a unilateral gland dissection at a later time with no tumor found in the glands. The fifth patient had a local excision, x-ray to the groin, and radon to the vulvar lesion. Local recurrences were treated on several occasions. She has survived for 15 years without further recurrence. All of these were early lesions.

This then would seem to represent the curative possibilities of an individualized therapy based upon simple vulvectomy followed at various intervals by local inguinal and femoral gland dissection and irradiation of various sorts.

There are good theoretical reasons for excluding irradiation as an effective attack. In this group, it seems to have been without curative effect except under the most unusual circumstances of localization and small early tumor.

In the second group treated since September, 1938, there were 44 patients. Two of these may reasonably be excluded from consideration. One presented complaints of persistent pruritis and the finding of kraurosis. Biopsy showed no tumor. A simple vulvectomy was done, and the routine sections of the surgical material showed no tumor. Further search was done by the department and an extremely early carcinoma found. It was decided to do nothing further, and the patient is alive and free of tumor 70 months after operation. The second patient was 80 years of age and could scarcely walk. She had trophic ulcers on both lower legs. She had an undifferentiated squamous cell carcinoma which involved the lower part of the anterior vaginal wall and the lower portion of the vestibule and urethra. From histologic appearance this

was more likely a carcinoma of the vagina. It is doubtful where it belongs, but it was treated by local excision and radon seeds. It has recurred and been retreated, but the patient is alive with recurrence which has been retreated after forty-one months.

This would leave 42 patients of whom 38 were treated by radical vulvectomy for an applicability rate of 90.5 per cent. Four patients were not treated. One was 63 years old and had been treated elsewhere by local vulvectomy followed by x-ray to the groins. There was a large mass of involved inguinal and femoral glands and a large tumor mass which extended the whole right side of the abdomen. She died in three months of carcinoma. The second

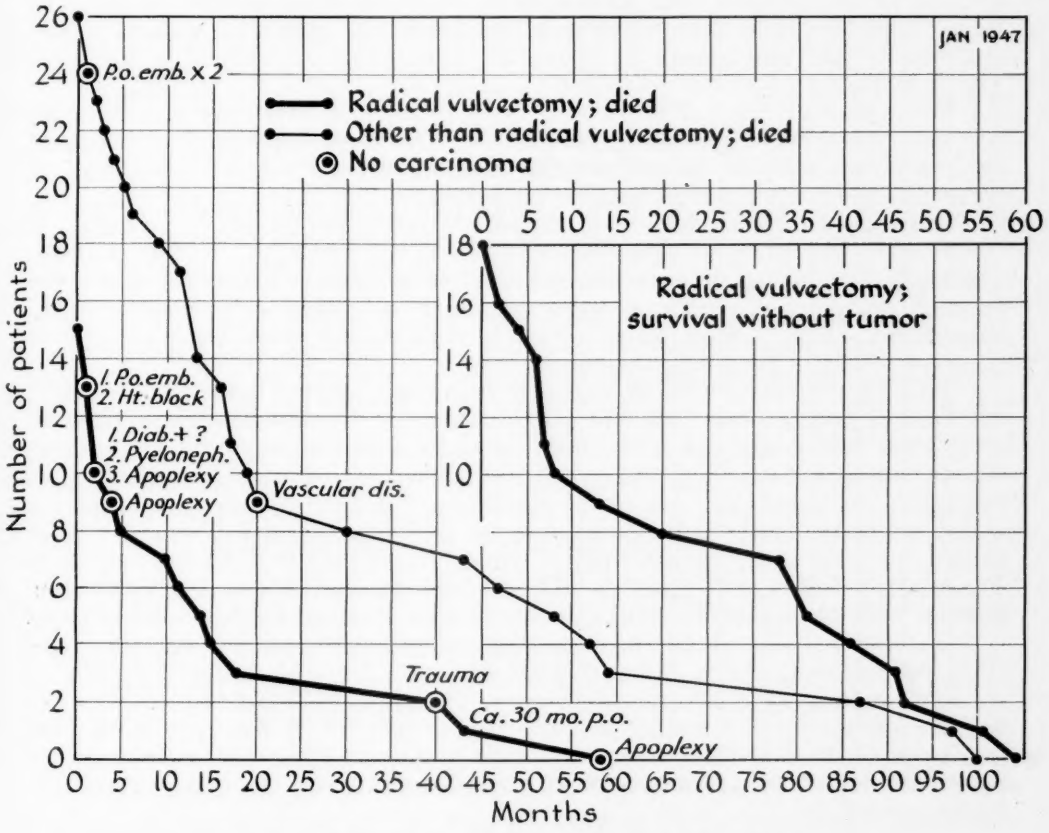

Fig. 1.—Survival of treated carcinoma of the vulva.

was 82 years of age, had a 10 cm. tumor, was obese, and showed advanced senility. She died in six months of carcinoma. The third was 84 years old and had been treated elsewhere by local excision, x-ray, and radium. She had a large tumor involving both labia, vestibule, clitoris, urethra, and the lower 4 cm. of the vagina. She also had pernicious anemia and was so senile that her answers to questions were quite irrelevant. She died seven months later of carcinoma. The fourth was a 40-year-old prostitute with a treatable tumor. For reasons of her own, she refused surgical therapy. She is alive with the tumor sixty-two months later!

Of the 38 patients who were treated by radical vulvectomy, 15 have died. Of these, four must be charged as postoperative deaths for a mortality rate of 10.5 per cent. One of these was 63 years old and had a tumor 2 cm. in diam-

eter involving the labium majus and minus on one side. She died of a pulmonary embolus on the twenty-second postoperative day. One was 84 years old, developed uremia due to pyelonephritis, and died on the forty-first postoperative day. She had a 6 cm. tumor of one labium majus. One was 74 years old with a 6 cm. tumor of labium majus and minus and metastatic tumor in the inguinal and femoral glands. She had diabetes and a bundle branch block before operation. She died of cardiac failure on the sixteenth postoperative day. The fourth was 73 years old and had a 2 cm. tumor of the labium majus and diabetes. She simply faded away to die on the forty-third postoperative day with no adequate diagnosis. Autopsy was refused. It seems clear that in all of these, the operative procedure was responsible for at least shortening the life of the patient. All have survived the operative procedure itself to die of complications later. However, whatever one may conclude as to the propriety of the indications for operating upon these patients, it would seem wise to consider the 10 per cent operative mortality as real.

Four patients have died at two, four, forty, and fifty-nine months after operation of other than malignant disease. None of these had evidence of recurrent tumor at the time of death. One other patient is alive and has recurrent tumor forty-six months after operation.

Only seven of those who were exposed to radical vulvectomy have died of carcinoma. The survival rates for these are shown in Fig. 1. There will undoubtedly be more as time passes, but it is not possible that this will reach the proportion dying of carcinoma after treatment by lesser means than radical vulvectomy. One is tempted to conclude that radical vulvectomy is a fairly effective means of removing the carcinoma.

This conclusion is further supported by the group of four who are alive and free of tumor more than five years. There are 15 patients who were seen more than five years ago and since the radical vulvectomy was introduced. Two of these were among those described above as untreatable. There were two operative deaths and the microscopic tumor treated by simple vulvectomy and described above. Of the remaining ten patients, four are alive and free of tumor, and two died without tumor but of other causes. There were then 4 carcinoma deaths of 10 patients who survived the radical vulvectomy by comparison with 23 carcinoma deaths of the 30 who survived the lesser procedures.

There are 18 patients who have had radical vulvectomies and who have survived without tumor from two to fifty-nine months. The duration of survival of these is shown in the insert in the upper right of Fig. 1. One can use various means to calculate the expected proportion of five-year cures from this group. This is inaccurate but, from whatever approach, it is apparent that the radical vulvectomy will produce several times the cure rate of the lesser procedures.

There are two melanosarcomas in this series, both of whom have had radical vulvectomy and who have survived without recurrence for thirty-six and forty-two months.

Some conclusions appear to be justified. The various types of therapy which do not include a single stage removal of inguinal and femoral glands intact with the radical removal of vulva and adjacent structures when necessary, will produce only about 15 per cent of five-year cures. A considerable proportion of patients so treated will survive for quite long periods of time as will those who are not treated at all. Because of the nature of the disease and the nasty symptomatology, this survival is a questionable advantage.

There is no evidence from this material that irradiation in any form has played any significant role in curing the lesion. It appears to be even less useful as a palliative measure. There are valid theoretical reasons for this.

Radical vulvectomy has improved the results significantly. Just what can be done with it is still open to question, since it has been applied here to 90 per cent of the tumors seen. Many of these were tumors which had been treated elsewhere by means which not only wasted considerable time, but interfered with the effective application of radical vulvectomy. Many were tumors which were only referred for treatment late in the course of the disease and who were treated mainly for palliative purposes. Sufficient time has not yet elapsed to justify relating the size of the tumor and its position to results which can be obtained by radical vulvectomy. That this is the most important feature affecting results is perfectly clear and, for what it may be worth, it can be said that in our experience, early carcinoma of the vulva other than that of the clitoris, is curable in a very large proportion of instances if radical procedures are undertaken at once. There has been sufficient experience with early tumors treated by other than radical vulvectomy to make it clear that minor procedures are not satisfactory. Local excision or local irradiation has no place in the treatment of early tumors. It seems clear that carcinoma of the vulva, particularly that of the labia majora, is a generalized disease and that the multiple nodules or recurrences are more often new areas of tumor than metastases or residual tumor from the main mass. To remove the vulva alone is to fail to take advantage of perhaps the most important clinical feature of the disease, which is the fact that lymphatic metastases tend to remain for reasonably long periods of time in the inguinal and femoral areas without spread beyond this. The presence or absence of palpable glands is no useful criterion as to presence or absence of tumor in this area. Contralateral gland involvement is so well known that the bilateral gland removal needs no support here. In view of all of this, it seems justified to conclude that the early cases should be treated by radical vulvectomy, and experience with this has shown it to be remarkably effective.

One would like to energetically oppose the carrying out of gland removal for biopsy. It serves no useful purpose since the glands are to be removed intact later. It involves opening into possible tumor-bearing tissue. It can make clean removal of the gland-bearing mass impossible.

It is hard to prove or disprove the wisdom of using radical vulvectomy in the advanced tumors. Survival rates for lesser procedures are shown in Table I. One suspects that those who experienced the longer survivals might have been cured by more radical approach although this cannot, of course, be proved. Otherwise, the survival rates for the lesser procedures and for radical vulvectomy are similar. To rid the patient even temporarily of ulcerated stinking masses is to make a significant contribution to their welfare. Surprising results are not unusual, and there are several patients among those who are surviving without tumor for long periods of time who were refused any interference by competent gynecologists. The applicability rate of radical vulvectomy here reported is an expression of the policy of applying it wherever even a reasonable hope of palliation exists. It appears to be justified. Statistical proof of the propriety of this must be postponed.

There are a number of unsolved problems. A large proportion of the wounds break down as a result of skin necrosis. This has been ascribed to various causes. A number of procedures have been tried in an attempt to avoid this. Leaving the wound open and applying dermatome grafts at the original operation made no improvement. Pressure dressings have only partially improved the results. The use of penicillin and the sulfonamides has not changed it. Experience has made it clear that the less undermined skin which is left the better the primary healing will be. It is wrong to sacrifice the wide removal of lymphatic-bearing fat or to attempt to excise the vulva or vagina too close to the tumor for the purpose of obtaining healing. Subsequent skin grafting or secondary closure is a satisfactory substitute, although this involves prolonged hospitalization in preparation for it.

In view of the fact that there are three deaths from embolism among the 80 patients, consideration will have to be given to vein ligation at the time of radical vulvectomy. This has not yet been done.

Extension of the operation to include removal of lymphatic structures along the femoral and iliac vessels within the pelvis, as has been advocated, has not been done for various reasons. One finds it hard to believe that this would be applicable to more than a few of the younger patients. It is a formidable operation, and if this involves the sacrifice of the single stage bilateral femoral and inguinal gland removal without cutting through the lymphatic bearing area, it does not satisfy the requirements which seem to be indicated in this study. There is no acceptable proof available at present as to the operative mortality involved but it is reasonable to assume that it will be considerably higher than that of radical vulvectomy as here described, if it be applied to other than an occasional selected patient. The numbers which can be cured when pelvic gland involvement is demonstrated are not yet known. The most serious argument against it lies in the fact that of the seven patients in this series who died of carcinoma following radical vulvectomy, every single one had local tumor on the surface of the vulva, symphysis, groin or vagina. Perhaps when we have learned to control this, it will be time enough to consider intrapelvic gland dissection.

It would appear from this material that the criterion of the five-year cure rate is a useful and reasonable expression of the results of treatment of carcinoma of the vulva.

Summary

1. Carcinoma of the vulva treated by a wide variety of combinations of simple vulvectomy, radium and x-ray, and with or without later unilateral or bilateral superficial or superficial and deep inguinal gland dissection produced an absolute cure rate of 13.9 per cent and a relative cure rate of 15.6 per cent.

2. In a second series, radical vulvectomy as described was applicable to 90.5 per cent. Of 38 patients so treated, 4 are alive and well more than five years after operation and 18 are alive and free of tumor for from two to fifty-nine months. This represents a significant improvement.

3. Some of the problems of the treatment of carcinoma of the vulva are discussed. Reasons are presented for the choice of this type of radical vulvectomy as opposed to lesser procedures and to further extension of the operation.

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Discussion

DR. R. E. CAMPBELL, Madison, Wis.—Dr. McKelvey is to be commended for this thorough study of carcinoma of the vulva, especially at a time when its treatment is in such a state of flux. I quite agree with him that at the present time there are as many different types of treatment as patients. It is only by studies such as this, in which the critical analysis has been both destructive and constructive, that treatment in medicine can go forward.

I have had a considerable experience with carcinoma of the vulva, having seen in the last twenty years probably over 100 cases. Earlier in my experience I was in the same dilemma as everyone else concerning the treatment of this condition. However, with the advent of Dr. Taussig's monumental reports of his experiences by radical surgery, I developed a new enthusiasm for treating this condition, and certainly the patient was given a new lease on life. Because of limitation of time I was unable to get a report of my cases to give at this time, but it is my intention to reflect my experiences in this discussion.

Dr. McKelvey has shown that in patients treated prior to 1938 the results were anything but favorable; in 32 of the 36 cases none was treated by radical vulvectomy and in this series there were 25 deaths and only 5 patients were alive and cured at the end of five years. The answer to these results is so obvious in comparison with the results of cases treated from 1938 to 1946 by radical surgery that it needs no further comment.

It is of greatest importance to note that in the series of 38 cases treated by radical surgery, there were only 15 deaths, 4 of which were charged as postoperative deaths, giving a mortality rate of 10.5 per cent. A great deal of emphasis should be placed upon the fact that four patients of this series are alive and cured after a five-year period, 18 are alive with no tumors from 2 to 59 months following treatment but it must be realized that undoubtedly some of these may succumb to the disease later on. One patient has had a prolongation of life of 46 months with a tumor still present. In further analysis of these figures it can be said that in the series of 38 cases treated by radical surgery, 22 are alive with no tumor, giving a percentage cure of 59 per cent at the present time, and this result is commendable.

Local anesthesia is important in these cases but infiltration of the tumor must be avoided. Dr. McKelvey uses two operative teams in his gland resections which is an excellent procedure for saving time.

So far as radiation therapy is concerned, I agree that it may be coupled with radical surgery in the more extensive lesions. In the radical operation where the glands are highly malignant, postoperative radiation therapy possibly might be indicated. It may also be the choice where patients refuse surgery, as it does have some palliative value.

It may be of interest that in my cases I have commonly left the vulvectomy wounds wide open without attempting to close them and it is remarkable how they will granulate in and epithelialize over. The blood proteins in these patients are carefully watched be-

cause of the considerable amount of serous drainage, and plasma may be administered in some cases. The patients are allowed to be on their feet forty-eight hours after operation and are discharged within a few days when the wound looks comparatively clean. The patients are given an ointment of 5 per cent boric acid and scarlet red to apply locally and they are advised to abduct their limbs.

In conclusion, I wish to state decisively that radiation therapy has little value in the treatment of carcinoma of the vulva and that radical surgery has been my treatment of choice as carried out by Dr. McKelvey.

I wish to take this opportunity to thank the Chicago Gynecological Society for the privilege of discussing this paper, and once again wish to commend Dr. McKelvey on his timely presentation.

DR. H. O. JONES.—Dr. McKelvey suggests that ineffective measures of treatment and inaccurate reports make systematic study of results impossible. This is especially true of the more or less rare diseases. No one clinic has a sufficient number of such cases to offer an accurate statistical report. Should such methods as suggested in this paper be followed, combinations of different reports would be most valuable.

We have followed the procedure advocated by the essayist and are quite certain the incomplete operation is inadequate. Recently we have had a patient die from hemorrhage due to erosion of the femoral artery by a metastatic carcinomatous nodule in a lymph gland treated at another hospital by the incomplete operation. We agree, furthermore, that x-ray is of little demonstrable value. We differ in our outlook upon the prognosis depending upon the location of the malignancy. We believe it is directly proportionate to the presence of lymph node involvement. It is true the areas mentioned by McKelvey are more prone to extension than those more favorably situated. Furthermore, as Taussig has pointed out, the cell type is of utmost importance. We believe, as he did, that the carcinoma in situ rarely, if ever, can be identified. It is, as Bowen's disease, relatively benign. So we must agree again with the author and Taussig that the real improvement in cures depends upon how early the diagnosis is made and how thorough the treatment.

More than 60 per cent of our cases have been associated with leucoplakia of the vulva and, having seen these lesions develop while x-ray and palliative procedures were being applied to the leucoplakia, we have treated this lesion radically.

I would urge all to join with McKelvey and standardize our reports to conform to a pattern to further the studies of this malignant disease.

DR. EDWARD ALLEN.—I would like to hear Dr. McKelvey say something about the preoperative treatment of these patients.

DR. McKELVEY (Closing).—There is little to add about the use of local anesthesia that has not already been said. We have been more worried about the possibility of disturbing the tumor itself than we have with the question of healing. I am satisfied that healing has no relation to the anesthesia. That is said for many reasons. In cesarean section, local anesthesia produces wounds that heal satisfactorily. Experience with the use of local anesthesia in simple vulvectomy in which there is a comparable degree of local removal of tissue produces complete healing. The surgeon treating melanosarcoma of the lower extremity does a similar inguinal dissection that follows the lymphatics down somewhat farther into the leg than we feel justified in doing. These are done under general anesthesia and produce exactly the same lack of primary healing. Careful observation of these wounds leads to the following conclusions. The amount of undermined tissue that has to be left behind will determine the proportion of skin breakdown. Where breakdown occurs there is first reddening of the skin associated with edema. Very gradually that skin becomes dusky and necrotic and sloughs away on the seventh to tenth day. Blueing appears on the fifth day. We are dealing here with a vascular problem of some sort. We thought at first it was a disturbed lymphatic supply which interfered with the blood supply, but I am not sure that is the explanation. I am sure it is not related to the local anesthesia.

It is clear that radical vulvectomy is applicable to a much larger proportion of patients than has previously been thought possible. Many of these are poor surgical risks and one does not dare to give them prolonged general anesthesia. It is our conclusion that the main feature in allowing wide applicability is the relative safety of the local anesthesia.

As to preparation, we do nothing locally to prepare for the operation. The tumor cannot be sterilized. We are dealing with an essentially infected area and cannot avoid it. Preoperative sulfonamides and penicillin have not been effective. All these patients carry retention catheters, and it has been our practice to use penicillin starting immediately after operation and add sulfonamides as soon as the urinary output has been established at 1,000 c.c. in twenty-four hours.

The preparation for local anesthesia is important. We begin sodium amytal preparation well ahead of time. The patient is given 6 grains of sodium amytal three hours before operation. One and one-half hours later the patient is seen and, depending upon the age and size of the patient and the estimated degree of sensitivity to barbiturates, another 3.0 grains of sodium amytal may be given. Hyosine, $\frac{1}{150}$ grain, is given when the patient is called to the operating room. Two-thirds of the patients have no memory of the operation. They wake up and wonder why the dressing is on. It is necessary to reinject with anesthetic solution under direct vision when the sensitive areas of the inguinal and femoral canals and the region of the clitoris are exposed. Occasionally extra morphine or demerol is given during operation.

The postoperative care involves the usual things. We use pressure dressings and we get the patients up and walking the day of operation.

THE CHARACTERISTICS OF UTERINE BLEEDING FOLLOWING CYCLIC ORAL THERAPY WITH ESTROGEN AND PROGESTERONE*

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THE effects of estrogen and progesterone therapy on the latent period and on the duration of uterine bleeding in monkeys have been studied in considerable detail.[1] Since the cycles of monkeys in many respects resemble those of women,[2] these data on the monkey have been translated to woman without complete experimental confirmation. The general impression of those working with rhesus monkeys is that the latent period after estrogen-progesterone treatment is shorter and less variable than that after treatment with estrogen alone. These observations in part have been confirmed clinically by Palmer[3] who observed that "although the estrogen withdrawal bleeding interval has been found to be quite constant in patients with primary amenorrhea and natural menopause, this is not the case in women with varying degrees of ovarian function exhibiting normal or abnormal menstrual cycles." Other observations on monkeys indicate that there is no difference in the duration of bleeding or the latent period following different levels of estrogen therapy.[4] Palmer,[5] from the study of eight amenorrheic or postmenopausal patients under treatment for a total of 19 cycles, concluded that the latent period was consistent regardless of variations in dosage and of methods of administration. Lastly, it was shown in monkeys that the duration of bleeding is longer after estrogen-progesterone treatment cycles than after estrogen treatment cycles.[1, 4]

For a number of years, patients have been treated in the Endocrine Division for functional disturbances of uterine bleeding with various schedules of cyclic, oral steroid therapy.[8] Analysis of the treatment data of some of these patients provides considerable information on the character of the latent period and on the duration of bleeding following estrogen and estrogen-progesterone oral therapy.

Method of Study

The material of this study concerns 276 cycles of 86 patients. For purposes of statistical analysis the patients were divided into four groups according to their history of bleeding:

Group 1. Patients with irregular, profuse and prolonged uterine bleeding.
Group 2. Patients with cyclic, profuse and prolonged uterine bleeding.
Group 3. Patients with infrequent and scanty uterine bleeding.
Group 4. Patients with absence of uterine bleeding for at least a year (amenorrhea), or failure of occurrence of menarche.

*Part of the expenses incurred in these studies was defrayed by grants to one of us (E.C.H.) from Ayerst, McKenna, and Harrison, Ltd., New York, N. Y. and from the Research Council of Duke University.

Several therapeutic schedules were employed:

1. Cyclic estrogen therapy consisting of the daily oral administration of 3.75 mg. of conjugated estrogens (premarin) or 3.0 mg. of diethylstilbestrol from the fifth to the twenty-fifth day of the cycle. Henceforth this will be referred to as cyclic E treatment.

2. Daily administration of 7.5 mg. premarin or 6.0 mg. of diethylstilbestrol from the fifth to the twenty-fifth day of the cycle. This will be referred to as double-E therapy.

3. The administration of 3.75 mg. of premarin or 3.0 mg. of diethylstilbestrol daily from the fifth to the twenty-fifth day of the cycle and 30 mg. of anhydrohydroxyprogesterone (pranone) daily from the fifteenth to the twenty-fifth day of the cycle. This will be referred to as E + P therapy. In a few instances, double-E + P also was used.

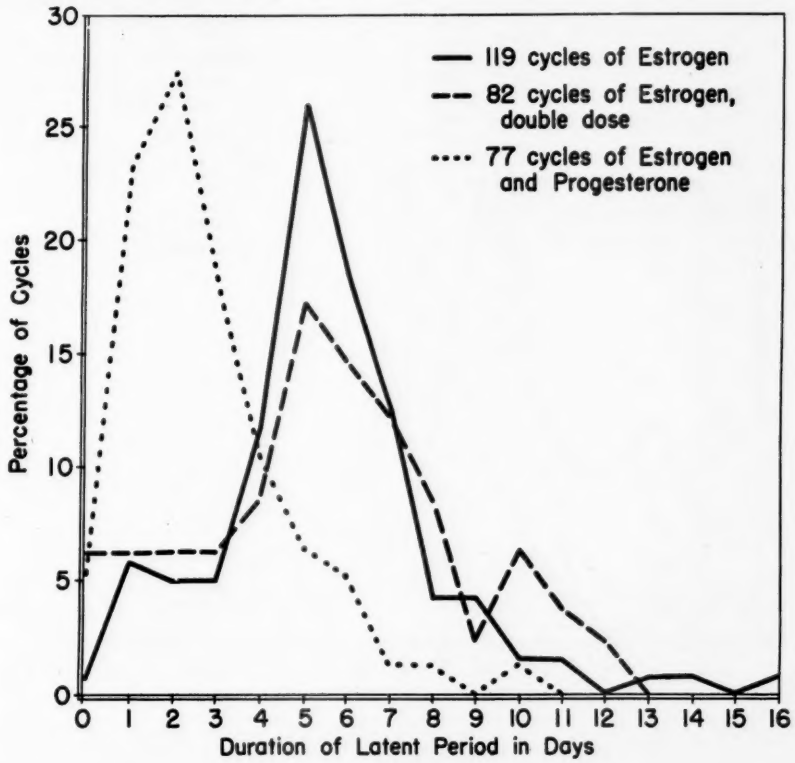

Fig. 1.—The effect of cyclic estrogen or estrogen and progesterone on the duration of the latent period.

The various correlations of latent period and of the duration of bleeding to the type of treatment and to the nature of the functional disorder then were plotted and analyzed for their statistical significance. In these calculations all cycles in which breakthrough bleeding occurred during treatment or bleeding failed to occur after therapy were excluded.

Results

Choice of estrogen: It was important to determine at the very beginning of this study whether or not the choice of natural (premarin) or synthetic (diethylstilbestrol) estrogen made any difference in the data. Statistical anal-

ysis failed to reveal any difference, and, in all further calculations, the type of estrogen used was disregarded.

Duration of the latent period; variation with different hormone schedules: The data are presented graphically in Fig. 1. In this section the character of the disturbance requiring treatment was not considered. It is evident that the patients treated with E + P bleed much sooner than those treated with E alone. This difference is statistically significant. The profound effect exerted by progesterone is illustrated by the following figures. The mean latent period with cyclic E is 5.4 days. whereas that with cyclic E + P is 2.7 days. With *estrogen alone* only 28.5 per cent of patients bled within the first four days and 68.9 per cent started to bleed between the fourth and eighth days.

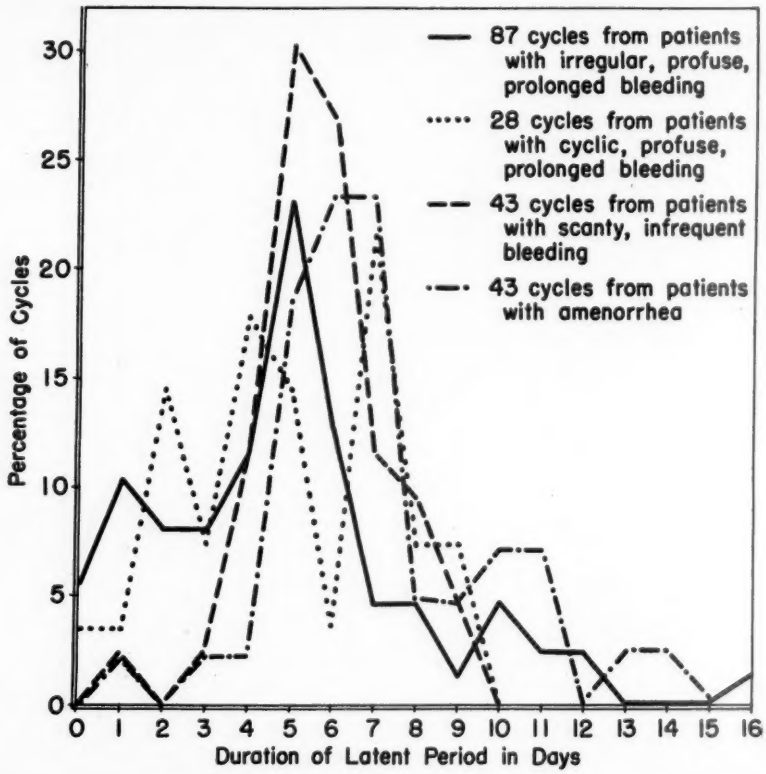

Fig. 2.—Duration of the latent period following cyclic estrogen therapy, and the influence of the type of functional disturbance under treatment.

Ninety-five and seven-tenths per cent had started to bleed within the first ten days after estrogen withdrawal. By comparison, 84.4 per cent of patients started to bleed within four days after the end of E + P *therapy* (74.4 per cent within three days) and in only 23.4 per cent did bleeding start between the fourth and eighth days. Ninety-six and one-tenth per cent started to bleed within six days after the end of treatment.

There is some difference (not statistically significant) between the curves of patients treated with cyclic E and double E. This difference concerns the height of the curve and not its general shape. This may be explained in part by the fact that double E was given usually during the first cycle of treatment. It is, of course, less likely that these first attempts at cyclic regulation should yield as homogeneous data as do subsequent cycles. This has been shown previously by one of us (E. C. H.).[6]

Duration of latent period; variation with the character of the functional disturbance: It is obvious from the foregoing section that the E and E + P groups cannot be considered simultaneously when studying the latent period. There were not enough E + P cycles available in each subgroup, based on the nature of the functional disturbance, to yield statistically significant data. Therefore, only those patients treated with cyclic E and double E are considered. Fig. 2 presents these data. The irregularity of the curves, in large measure, is due to the relatively small number of cycles available for study.

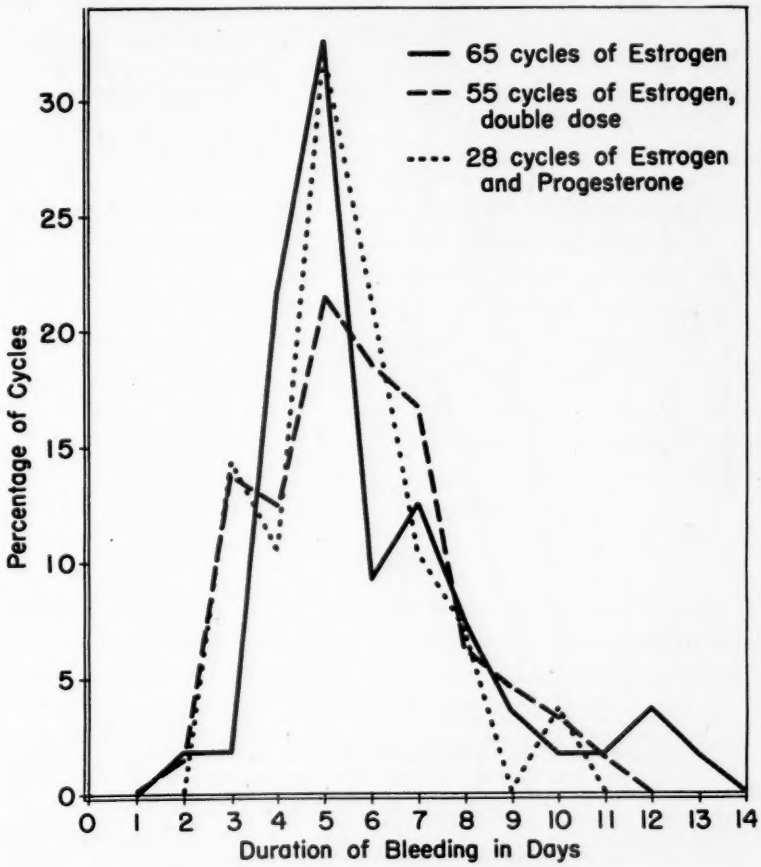

Fig. 3.—The effect of cyclic estrogen or estrogen and progesterone on the duration of uterine bleeding.

For this reason, frequency distribution figures, for the most part, were not statistically significant. One important feature is observed, however: 43.5 per cent of patients with irregular excessive bleeding and 46.4 per cent of patients with cyclic excessive bleeding had a latent period of four days or less following estrogen therapy. These data contrast with those of patients with infrequent scanty bleeding and amenorrhea, of whom only 16.4 per cent and 6.9 per cent respectively bled within the 4 days after the withdrawal of treatment. These data are statistically significant.

Duration of bleeding; variation with different hormone schedules: These data are presented in Fig. 3. The addition of progesterone to the treatment did not increase the length of the period of bleeding, contrary to observations on experimental animals. The slightly different appearance of the double-E

curve is explained by the fact that this was usually the first cycle of treatment and, accordingly, effects of the previous functional disturbance persisted. The mean duration of bleeding of patients treated with cyclic E was 5.2 days; 83.1 per cent bled from three to seven days. With double E the mean duration was 5.5 days and 78.2 per cent from three to seven days. With E + P the mean duration was 5.4 days and 89.3 per cent bled for three to seven days.

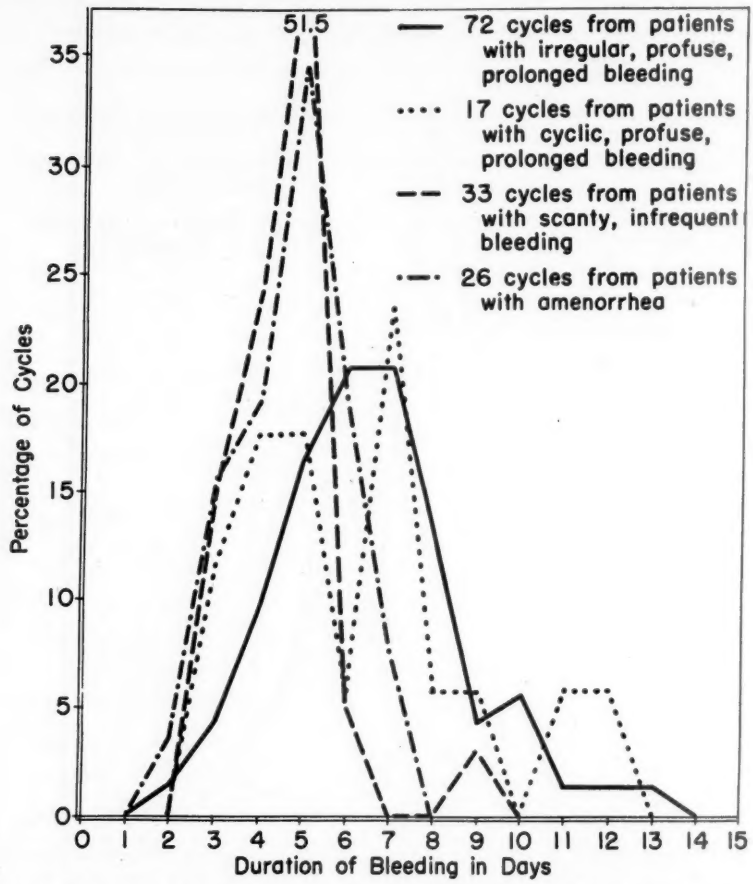

Fig. 4.—Duration of uterine bleeding following therapy, and the influence of the type of functional disturbance under treatment.

Duration of bleeding; variation with the character of the functional disturbance: The entire group of patients is included in these calculations (Fig. 4) inasmuch as it was shown that the duration of bleeding was unaffected by the treatment schedule (i.e., whether E or E+P). The curves show clearly that those patients treated for excessive bleeding continue to bleed for relatively longer periods than those patients who originally had infrequent and scanty or absent periods before treatment. Those patients under treatment for irregular excessive bleeding and for cyclic excessive bleeding bled for a mean of 6.5 and 6.3 days, respectively. Bleeding lasted for three to six days in 51.4 per cent of the former group and in 53.0 per cent of the latter group. By way of contrast patients under treatment for infrequent scanty bleeding and for amenorrhea bled for a mean of 4.6 and 4.7 days, respectively. Bleeding lasted for three to six days in 96.9 per cent of the former and in 88.5 per cent

of the latter group. Statistical analysis confirms the unquestionable significance of these figures despite the relatively small number of cycles available in each group.

Discussion

Our data bear out observations in monkeys that the latent period after estrogen-progesterone treatment is shorter than that after estrogen treatment alone. On the average, the latent period was 2.7 days (50 per cent) shorter in the E + P group. On the other hand we did not find that the duration of bleeding was prolonged by the administration of anhydrohydroxyprogesterone, as it has been observed with progesterone by Cleveland[1] and Phelps.[4] It is possible that this difference resulted from the use of castrated animals.

Forty-three cycles of estrogen therapy were studied in patients with amenorrhea or failure of occurrence of menarche; the duration of bleeding was relatively constant but the latent period was not. Essentially similar observations were made on the group with infrequent scanty bleeding.

We were able to corroborate the statement of Palmer[3] that the method of administration did not have any effect on the nature of bleeding. In comparing our results from oral E + P therapy with similar schedules of E + P given parenterally which have been published elsewhere,[7] identical curves for the duration of bleeding were obtained. Our observations on the similarity of results following E and double-E therapy confirm the statements of Phelps[4] and Palmer[5] that there is no difference in latent period or duration of bleeding with different levels of adequate estrogen therapy.

Conclusions

1. The latent period after cyclic estrogen-progesterone therapy is shorter (mean 2.7 days) than after cyclic estrogen therapy alone (mean 5.4 days).

2. Patients under treatment for functional excesses of bleeding, bleed more promptly after estrogen withdrawal (43.5 per cent to 46.4 per cent in four days) than do those under treatment for infrequent scanty bleeding or amenorrhea (6.9 per cent to 16.4 per cent in four days).

3. Even under cyclic hormone therapy (E or E + P), patients with excesses of bleeding tend to bleed longer than those with infrequent scanty or absent periods.

4. Progesterone does not prolong the duration of bleeding in women treated for functional uterine disturbances.

5. Doubling the dose of estrogen did not affect the latent period or duration of bleeding.

6. The duration of bleeding is identical when estrogen-progesterone is given orally or parenterally.

7. The choice of synthetic (diethylstilbestrol) or natural (premarin) estrogen did not influence the latent period or duration of bleeding.

We express indebtedness to Dr. Donald S. Martin, Professor of Public Health and Preventive Medicine, for assistance in the statistical treatment of the material. Estrogens (premarin and diethylstilbestrol) were supplied for these studies by Ayerst, McKenna and

Harrison, Ltd., New York, New York. Anhydrohydroxyprogesterone (pranone) was supplied for these studies by Schering Corporation, Bloomfield, New Jersey.

This present study would not have been possible were it not for the exact and conscientious records kept by past members of the department.

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THE MANAGEMENT OF PROLONGED LABOR

A Four-Year Review From the Lewis Memorial Maternity Hospital

HERBERT E. SCHMITZ, M.D., JAMES X. BREMNER, M.D., JANET E. TOWNE, M.D., AND GEORGE R. BABA, M.D., CHICAGO, ILL.

ONE of the most trying complications of pregnancy confronting the obstetrician is the management of prolonged labors. The designation prolonged labor is an arbitrary one and each investigator has his own criterion. Cosgrove and Glisson[2] set thirty-six hours as the limits of normal labor. Douglas and Stander[3] in their study of *Infantile Mortality in Prolonged Labors* used thirty hours as the limit. Kuder and Johnson[4] also used thirty hours in their study on *The Elderly Primipara.* On the other hand, Williams,[13] in his analysis of the 206 maternal deaths associated with prolonged labor, and Linn and Douglas,[5] in their treatise on *Prolonged Labor,* defined as prolonged any labor exceeding twenty-four hours' duration. We, too, have selected twenty-four hours as the limit of normal labor.

Further complicating the criterion of prolonged labor is the difficult differentiation between the so-called "false pain" and the "true pain." Patients may enter the hospital with apparently severe pain only to have the pain disappear entirely and the true labor not occur until several weeks later. On the other hand the patient may have "false pains" which may suddenly change to "true pains." Still further adding to the confusion is the factor of individual differences in the evaluation of labor pain by the various physicians or the residents examining the patients. These factors make any determination of the length of labor in a large series merely an estimate which cannot be entirely accurate.

Notwithstanding the variable and uncertain criteria for classification, the group of patients designated as "prolonged labor cases" poses a real problem in its management. If the attendant yields to the pleas of the patient or her family and attempts an ill-advised interference, he may do irreparable damage to her future chances of conceptions, and perhaps leave her in a state of chronic invalidism as well as further jeopardizing the mother and the infant in this present pregnancy.

Definition.—In this investigation, twenty-four hours has been selected as the limit beyond which the labor is considered prolonged. Labor was considered to be initiated with the onset of regular uterine contractions associated with pain, regardless of the presence or absence of effacement, dilatation of the cervical os, or the rupture of the membranes.

On estimating the duration of labor, we necessarily counted the elapsed time from the onset to the delivery. In the majority of the longer cases, there were some periods in which the patient was not having regular contractions.

*Read before the Chicago Gynecological Society, Jan. 17, 1947.

but most of these patients were suffering from backache. From the psychological and practical standpoint, we feel that these patients must be considered in labor and treated as such.

Material Studied

In the four-year period between July 1, 1942, and June 30, 1946, 5,599 patients were delivered at the Lewis Memorial Maternity Hospital, the Obstetrical Teaching Unit of the Loyola University Medical School. Of these, 224 (or 4.00 per cent) patients had labor exceeding twenty-four hours' duration, and hence classified as prolonged labor cases. The cases excluded obstructed labor due to complicating tumor or disproportion, and were confined to those instances in which normal progress would be expected but which did not materialize. We feel, in accord with the findings of Calkins[1] and Murphy,[2] that presentation and position do not materially influence the first stage of labor in the majority of the cases. They do however, play a more important part in the second stage and its management; hence we have included the cases of brow, breech and transverse presentations in our figures.

Management

The patients were for the most part handled by the resident staff under the direct supervision of the senior staff member in charge of the prolonged Labor Service in accordance with our established routine. The routine procedure is based on extreme conservative management directed toward anticipating and combating infection and exhaustion during the antepartum phase, and maintaining a constant vigil for hemorrhage and shock during the postpartum phase.

As it is an established fact that the incidence of infection is increased as the duration of labor is lengthened, particularly after the rupture of the membranes, rectal and vaginal examinations are kept to a minimum. Every effort is made to avoid vulval contamination during rectal examinations, and all vaginal examinations are made in the delivery room under strict aseptic technique.

We attempt to combat dehydration, starvation, and exhaustion by the early institution of a dietary regime which includes small feedings of a soft diet every four hours. Liquid intake by mouth is encouraged. In the event that the patient is unable to retain food or liquid by mouth, 1,000 c.c. of a 5 per cent glucose in saline solution is administered twice a day or oftener, if indicated. Exhaustion is combated by an eight-hour period of rest alternating with a like period of labor. Morphine sulfate was the drug of choice in these cases as the barbiturates not infrequently caused excitation in the patient.

When labor has been in progress for twenty-four hours, the urine is examined every six hours for acetone and albumin and the fluid output checked carefully. In the event of the appearance of acetone and di-acetic acid in the urine, with a rising pulse rate and signs of impending collapse, the patient is heavily sedated and placed on continuous fluids. With the proper early treatment and management, we feel that the danger of collapse is minimal.

During the period following the sedation the labor usually progressed without stimulation. In few instances, intravenous calcium gluconate, quinine, and rarely small doses of pituitrin were used. The majority received no artificial stimulation.

Delivery was not attempted in any case until the first stage was terminated and the cervix completely dilated. Major operative procedures were discouraged during the second stage unless the conditions and indications warranted interference.

Following delivery, the patient is kept in the delivery room under sterile drapes for a period of one hour. The blood pressure is checked every fifteen minutes or oftener if indicated. Early use of plasma and whole blood are encouraged. Intrauterine packs are used to control hemorrhage when needed, but such procedure tends to increase the danger of infection.

Results

The results of our study are depicted on Tables I to XII. Table I shows the cases grouped into twelve-hour periods from twenty-four to one hundred and eight hours and the relative frequency of each period. In Table II the distribution is according to age, and in Table III according to parity. It is significant that the primigravidas represent the majority of the cases. Table IV further subdivides the primigravidas into age group. In Table V is shown the position and presentations encountered. In this grouping, we find that 164 cases presented as occiput anterior, 18 as persistant occiput posterior, and 19 as deep transverse arrest. Table VI gives the classification of the type of pelvis based on the impression and measurements of the examining physician. Table VII is self-explanatory, and describes the types of delivery encountered. Table VIII reveals the damage to the perineum and cervix in this series. The com-

TABLE I. LENGTH OF LABOR

DURATION IN HOURS	24-36	37-48	49-60	61-72	73-86	87-96	97-108
Number of cases	140	50	20	7	5	1	1
Percentage	62.5%	22.3%	8.9%	3.1%	2.2%	0.44%	0.44%

TABLE II. AGE DISTRIBUTION

AGE GROUPS	16-19	20-29	30-39	40-45
Number of cases	27	141	47	9

TABLE III. DISTRIBUTION BY GRAVIDITY

GRAVIDA	I	II	III	IV	V	VI	VII	VIII	IX
Number of cases	155	29	16	9	6	4	2	2	1

TABLE IV. AGE DISTRIBUTION OF THE PRIMIGRAVIDAS

AGE GROUPS	16-20	21-25	26-30	31-35	36-45
Number of cases	36	59	39	12	9

TABLE V. PRESENTATIONS AND POSITIONS

CEPHALIC	BREECH	OTHERS
OLA – 93	LSA – 7	Transverse – 1
OLT – 6	LST – 2	Brow – 2
OLP – 8	LSP – 2	RMA & RMT
ORA – 71	RSA – 7	
ORT – 13	RST – 1	
ORP – 10	RSP – 1	

TABLE VI. "CLINICAL" CLASSIFICATION OF PELVIS

Normal gynecoid	207
Gynecoid with android tendency	10
Slightly platypelloid	3
Platypelloid	4
	224

plications encountered are shown in Table IX. Table X describes the morbidities encountered during the series. There were 22 morbid cases, or 9.9 per cent as compared with an over-all morbidity of 3.8 per cent. Table XI shows the prenatal complications met with in this group. Table XII compares the infant mortality in the group of prolonged labor cases with the total infant mortality in all cases delivered. It is significant that there is a marked rise in the percentage of infant mortality in the prolonged labor group.

Among the 5 599 cases delivered in the four-year period, 35 were elderly primiparas—that is, women 35 years or older who were delivered of viable infants for the first time. The age ranged from 35 to 42 years. The duration of labor varied from 5 hours, 4 minutes to 107 hours and 20 minutes with an average of 17½ hours. Seven delivered spontaneously, 11 were delivered by

TABLE VII. TYPE OF DELIVERY

Spontaneous	54	24.1%
Outlet forceps	82	35.6%
Low forceps	58	25.8%
Mid forceps	8	3.5%
Breech	10	4.4%
Breech extraction	8	3.5%
Version and extraction	3	1.3%
Manual correction of brow, low forceps	1	0.4%
Forceps correction of brow, rotation and extraction	1	0.4%

TABLE VIII. CONDITION OF PERINEUM AND CERVIX FOLLOWING THE DELIVERY

	I	II	III	IV	V	VI	VII	VIII	IX
Intact	1	5	6	3	3	2	2	1	1
Episiotomy	146	19	6	3	1	0	0	0	0
Episiotomy with Cervical laceration	3	0	0	0	1	0	0	0	0
1° Laceration	3	1	2	0	1	0	0	0	0
2° Laceration	0	2	0	2	0	2	0	0	1
2° Laceration c̄ Cervical laceration	1	0	1	1	0	0	0	0	0
2° Laceration c̄ Para-ureth. laceration	1	1	0	0	0	0	0	0	0
3° Laceration c̄ Cervical laceration	0	1	0	0	0	0	0	0	0
Laceration of Vaginal wall	0	0	1	0	0	0	0	0	0
	155	29	16	9	6	4	2	1	2 – 224

TABLE IX. COMPLICATIONS OF LABOR AND DELIVERY

Contraction ring	1
Intrapartum infection	1
Maternal exhaustion	11
Uterine inertia	12
Deep transverse arrest of the head	19
Persistant occiput posterior	18
Prolapsed cord	2
Transverse lie with prolapsed cord	1
Intrapartum hemorrhage	2
Postpartum hemorrhage	14
Postpartum hemorrhage and shock	2
Chill immediately postpartum	1
No FHT at onset of labor	3
Epileptic seizures during labor	1
Fetal distress	2
Vaginal bleeding due to placenta previa marginalis	1
Postpartum shock	1
Abruptio placenta	1

TABLE X. MORBIDITY

Mild endometritis	1
Endometritis	1
Endometritis and myometritis	1
Thrombophlebitis	1
Acute congestive mastitis	2
Pyelitis	1
Cystitis	1
Paralytic ileus	1
Intestinal obstruction	1
Infected episiotomy	1
Infected episiotomy & breakdown of wound	2
Abscessed tooth with cellulitis	1
Upper respiratory infection	2
Infected thrombosed hemorrhoids	1
Pyelocystitis	3
Unknown etiology	2
	22

TABLE XI. PRENATAL COMPLICATIONS

Mild hyperemesis gravidarum	2
Hyperemesis gravidarum	2
Mild hypertensive toxemia	9
Hypertensive toxemia	7
Marked varicosities of legs and vulva	2
Sinus arrhthymia	1
Rheumatic heart disease	1
Epilepsy	2
Cystitis	1
Pyelitis	1
Lues	1
Gastritis	1
Chancroid	1

TABLE XII. INFANT MORTALITY

Total number of deliveries	5599	Total number of prolonged labors	224
Total infant mortality incl. Prematures	146 (2.60%)	Total infant mortality incl. Prematures	16 (7.40%)
Fetal deaths	64 (1.14%)	Fetal deaths	5 (2.23%)
Stillbirths	82 (1.46%)	Stillbirths	11 (4.91%)
Corrected mortality	(1.66%)	Corrected mortality	(6.69%)

outlet forceps, 9 by low forceps, 3 by forceps rotations with low forceps extraction, and 5 elective cesarean sections of the low cervical type were performed. In this group of elderly primiparas, 9 (25.7 per cent) were cases of prolonged labor. Their ages ranged from 36 to 39 years. The duration of labor was 26½ hours to 107 hours, 20 minutes, with an average of 47 hours, as compared to the average length of 37.8 hours in the whole series of prolonged labor. The complications of pregnancy, labor, and types of delivery have already been indicated on the tables.

In the entire group of elderly primiparas (35 patients), the infant mortality totaled five cases (16 per cent), three fetal deaths, one of which was premature, and two stillbirths. It is interesting to note that four out of the five deaths occurred in cases of prolonged labor. In other words in nine cases of prolonged labor in women 35 years or older, 4 had dead babies (44 per cent) while in the remaining 26 cases there was only one stillbirth.

There was no maternal death in this series of 224 cases of prolonged labor.

Discussion

In reviewing the present series, we find that our incidence of 4.0 per cent compares favorably with Williams' incidence of 4.70 per cent, Huber's Chicago Lying-in incidence of 6.3 per cent and Cosgroves' Margaret Hague Maternity Hospital incidence of 5.9 per cent.

The causes of prolonged labor may be divided roughly into two groups: (1) those causing prolongation of the first stage of labor, and (2) those causing prolongation of the second stage. As Calkins[1] has pointed out, the first stage is involuntary and has to do only with the cervical effacement and dilatation, whereas the second stage is at least partly voluntary and has to do with the propulsion of the fetus through the birth canal.

In this series, we found that the incidence of prolonged second stage was very low, about 5 per cent of the cases having a second stage lasting over three hours. Operative interference, of course, is responsible for the shortening of the second stage in a large percentage of the cases, so that we have no way of determining how many more might have occurred.

The prolongation of labor is usually due to the prolonged first stage. The duration of the first stage is dependant on two main factors: (1) resistance of the cervix to dilatation, and (2) the all-important intensity and frequency of the labor pain. We do not feel that the position, the presentation, the size of the fetus, or the station of the presenting part are primarily the cause of prolongation of the first stage. It is our impression that a faulty and ineffectual type of pain is usually responsible. This is in accord with the findings of Murphy's work with the Lorand tocograph, which verified the conclusion of Calkins and others.

Prolonged labor due to cervical dystocia is usually due to congenital anomaly, severe scarring from previous trauma, or longstanding infections with resulting fibrosis or scarring. It is generally conceded by most writers however, that cervical dystocia alone is seldom the cause of prolonged labors. Cosgrove, in 1939, directed our attention to the infrequency of cervical dystocia requiring Dührrsen's incision, and our experience with this group of cases tend to bear out his finding, as we had no instance in which cervical incision was considered to be indicated. His over-all fetal mortality of 7 per cent coincides closely with our own uncorrected fetal mortality of 7.4 per cent.

In our group of elderly primiparas, although the number is too small for an adequate statistical study, it would seem that age presents a definite factor in the ability of the uterus to develop a vigorous type of contraction. Over 25 per cent of the group from 36 to 42 years of age developed prolonged labor.

Termination of prolonged labor by cesarean section carries a very high maternal mortality, as shown by Williams[13] in his analysis of 206 deaths in prolonged labor. In the event that this procedure be required, he recommends the Waters type of operation as being the least hazardous for the mother.

Conclusions

1. Prolonged labor is usually the result of an ineffectual type of uterine contractions.

2. There is a definite increase of fetal mortality in prolonged labor.

3. The morbidity rate is increased in patients which are in labor more than twenty-four hours.

4. The elderly primipara group shows a higher percentage of prolonged labor than the younger group.

5. The elderly primipara group in prolonged labor shows a marked increase in the fetal mortality over the younger age group.

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Discussion

DR. HENRY BUXBAUM.—I believe Dr. Bremner is erroneous on his assumption that his figures are comparable to those of Williams, Huber, and Cosgrove, inasmuch as he has utilized a different standard. In the first place he eliminated all cases of prolonged labor due to disproportion, which is a somewhat difficult thing to do, and, secondly, I would like to question his definition for the onset of labor. It has always been my opinion that labor is not considered initiated until there is some effacement and or dilatation of the cervix. The pains prior to this time may be considered as preliminary according to Hamilton. Therefore the similarity of the incidence of prolonged labor (4 per cent) between his figures and those cited is more apparent than real. Prolonged labor is beyond a doubt the most difficult complication to handle in the entire field of abnormal obstetrics and requires keen observation and sound judgment. When a situation such as this does arise it behooves the obstetrician to re-evaluate the case thoroughly. As to the mother, her pulse, temperature, blood pressure, pelvic architecture, and general physical condition. As to the fetus, position, presentation, size, attitude, station, and heart tones. And also as a means to determine what we can expect the woman to accomplish herself, we must resort to some one of the impression methods as Munro-Kerr, Mueller, or Hillis, or your own personal modification of one of these three methods. Dr. Bremner stated that, in his opinion, ineffectual uterine contractions are responsible for most cases of prolonged labor. This undoubtedly is true, but I do not believe we can entirely divorce this factor from two other closely related factors, namely, anomalies of the passages and anomalies of the passengers. As a matter of fact, he has an incidence of 10 per cent breech presentations in his series, besides 18 occiput posteriors, 1 transverse presentation, and 1 brow presentation. Many times, unfortunately, in my experience, not one, but all these factors are present to add to the difficulties of the obstetrician.

I agree with Dr. Bremner in his condemnation of the use of barbiturates in these cases. He uses morphine sulfate, we use demerol, both opiates. Barbiturates do not give the patient the necessary rest or relaxation, and renders her incapable of cooperating when this is most necessary.

I do not understand Dr. Bremner's hesitancy to perform Dührssen's incisions when indicated. Especially in a primigravida with the cervix completely effaced, more than seven

centimeters dilated, and the head well in the pelvis with no progress for six to eight hours, in spite of apparently adequate uterine contractoins. I believe it is less traumatic to both the mother and the child to terminate labor at that time than to allow her to go on an indefinite number of hours with the outcome still uncertain. These conditions when Dührssen's become necessary are relatively rare, but they do arise.

It is to be noted that in any unselected consecutive series of cases the incidence of cesarean sections would be much higher than these cited by Dr. Bremner, who had exactly none. This is indeed a compliment to his obstetric skill and judgment. At the same time I would like to point out that of the sixteen babies who did not survive, four occurred in his nine cases of elderly primigravida, those who could least afford to lose their child. If these deaths occurred during labor one might conjecture that these are the cases in which a cesarean section may have been indicated.

I should like to emphasize an excellent point Dr. Bremner brought out in his paper, and that is the extremely high incidence of postpartum hemorrhage following a prolonged labor. His series contained six cases, an incidence of 7 per cent, a fact which we should be cognizant of and be prepared to handle if necessary.

In conclusion, I would like to recommend, besides the sedation and parenteral fluids Dr. Bremner mentioned during labor, the use of vitamin K to the mother and the baby soon after delivery as well as the use of chemotherapy, especially if the membranes have been ruptured for any length of time.

DR. DAVID N. DANFORTH.—Dr. Bremner mentioned the use of calcium for purposes of stimulation in prolonged labor. I should be interested to know of his results with this therapy. In our experience calcium is of value only in selected cases, where all of the mechanical requirements for normal labor are fulfilled. It is not useful in cases where inertia can be ascribed to faulty fitting of the presenting part to the lower uterine segment, or as is often found in malposition or malpresentation, or where inertia may be due to improper alignment of the uterus to the pelvis. Where factors such as these cannot be demonstrated, calcium appears to be useful.

DR. BREMNER (Closing).—In regard to determining when labor actually begins, I pointed out that we are very much convinced that we must consider these cases psychologically in labor, even though there is no effacement or cervical dilatation. I realize that there is great controversy and difference of opinion in this matter. I neglected to include that in practically all of these cases vitamins were added to the medication.

Concerning Dührssen's incision, it so happened that we did not have any. Possibly there were cases in which that might well have been used. I personally rarely use Dührssen's incisions, I do not like them. That is probably why they were not done. We sectioned 35 per cent of our primigravidas that were over 35 years of age. The other primiparas that were not sectioned were those that we expected up to a certain stage would deliver normally, and after that we could not do cesarean section without producing maternal morbidity or increasing the risk of maternal mortality. I agree that psychiatric factors probably play a greater role than we now give them credit.

I believe it was Eastman who recommended small doses of pituitrin. He believed it stimulated uterine contractions and definitely improved his results. My own personal results with pituitrin are not good. I have had two cases in the past ten years that developed tetanic contractions.

Our success with intravenous calcium gluconate was extremely variable, so much so that we could not come to any accurate determination. It was used symptomatically, depending on the response. We do not have much to say either for or against it.

FETAL AND MATERNAL MORTALITY*

An Eleven-Year Survey

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ALTHOUGH great advances have been made in the practice of obstetrics in the past decade, there remains much room for improvement in procedure.

Stander,[3] in his vehement appeal for unification of obstetric and gynecologic teaching, pleaded for better instruction in obstetric practice in our schools of medicine. In this regard, one of his more pertinent arguments was the statement: "The family doctor usually does not practice surgery, and most frequently has time to consult another physician or internist. On the other hand, he invariably delivers women and cares for the ills of women. Thus he assumes a great responsibility in the lives of both mother and child." This statement is corroborated by the fact that the majority of women are delivered by general practitioners, who lack an adequate obstetric training. Surgeons, moreover, have invaded the pregnant uterus, performing cesarean section with doubtful indications and high maternal mortality.

For these reasons, we consider Stander's appeal opportune, and it is our purpose to show, by analysis of local figures, that observance of proper obstetric practice is a major means of improving obstetric results.

Material and Methods

This paper represents a compilation of the data collected in a survey covering an eleven-year period from January, 1935, through December, 1945, at the Department of Obstetrics, Bethesda Hospital, Cincinnati, Ohio. About 80 per cent of the patients were delivered by private physicians. The remaining 20 per cent are "service" patients and were delivered by interns and residents under the supervision of members of the obstetric staff.

In this study, only patients who were delivered in the hospital were included. Excluded also was a small group of patients whose pregnancies were interrupted prior to five months' gestation. These, for one reason or another, had not been admitted to the gynecologic service.

Although the main purpose of this study was the analysis of maternal and fetal mortality rates, we found it of interest to scrutinize the incidence of the various modes of presentation and the types of delivery. In order to obtained a clear conception of the variation in mortality, in relation to the degree of the physician's obstetric experience and training, the deliveries performed by obstetric specialists and general practitioners were separately listed.

During the eleven-year period, 15,088 patients were delivered. It is interesting to note that in the last three years (1943 to 1945) this rate was three times that of 1935. This emphasizes the great increase in the number of hospital versus home deliveries in recent years.

Incidence of Presentation.—Vertex presentation comprised 95 per cent of the total, and breech 4.4 per cent. Face, transverse, and brow presentations, respectively, comprised the remainder of these cases.

*Presented at a meeting of the Cincinnati Obstetrical Society, Oct. 17, 1946.

Type of Delivery.—Table I shows the incidence of methods of delivery, while Figs. 1 and 2 show their annual variations. During the last five years, considerable change has occurred in the obstetric routine. Low forceps delivery, our method of choice, has shown a steady increase (Fig. 1).

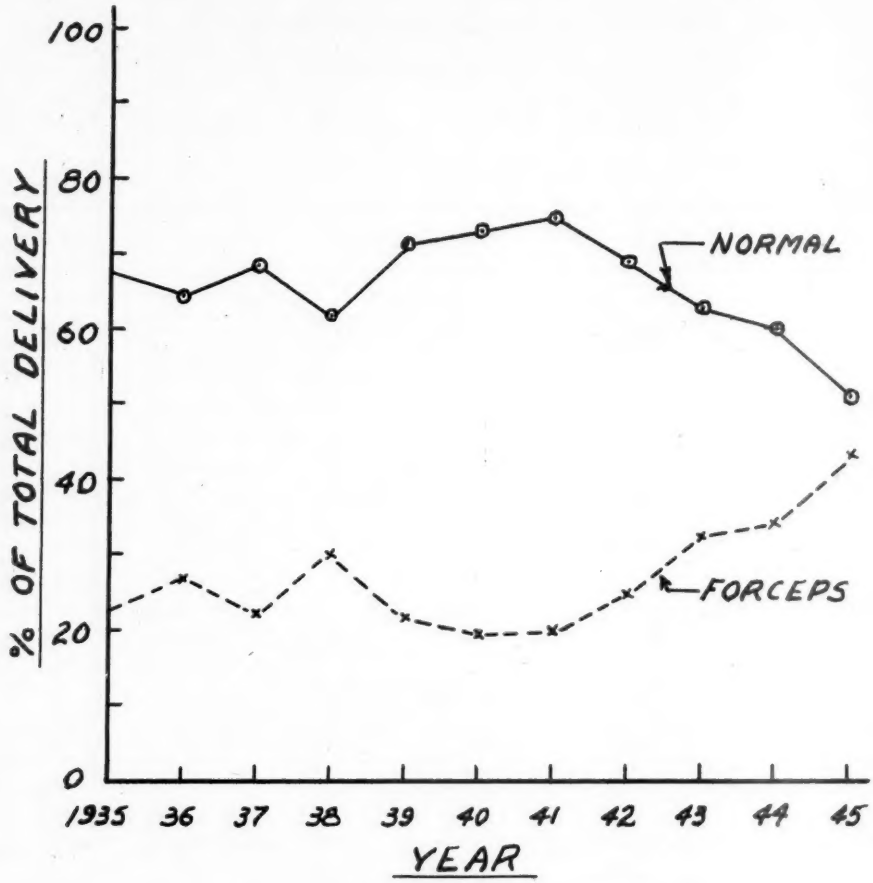

Fig. 1.—Relative incidence of normal and forceps delivery.

TABLE I. TYPE OF DELIVERY

TYPE OF DELIVERY	NUMBER OF CASES	PER CENT
Normal (vertex)	9,825	65.14
Forceps	4,282	28.38
Breech	656	4.34
Cesarean section	205	1.35
Version	120	0.79
Total	15,088	100.00

TABLE IA. TYPE OF FORCEPS DELIVERY

TYPE	NUMBER OF CASES	PER CENT
High	222	5
Middle	852	20
Low	3,208	75
Total	4,282	100

The most striking changes were observed in the annual rate of section and high forceps. Between 1935 and 1940, 85 per cent of the cesarean sections were performed by general surgeons in collaboration with general practitioners. In 55 per cent of these operations, the generally accepted criteria for cesarean sections were not demonstrated. In 1940, the Obstetrical Committee ruled that no section or high forceps delivery could be performed by any practitioner or surgeon without previous consultation with a qualified obstetrician. This important decision resulted in a steady decline in the number of deliveries by these two methods. In the last four years the average percentage of cesarean sections was reduced from 3 per cent to approximately 0.65 per cent. This

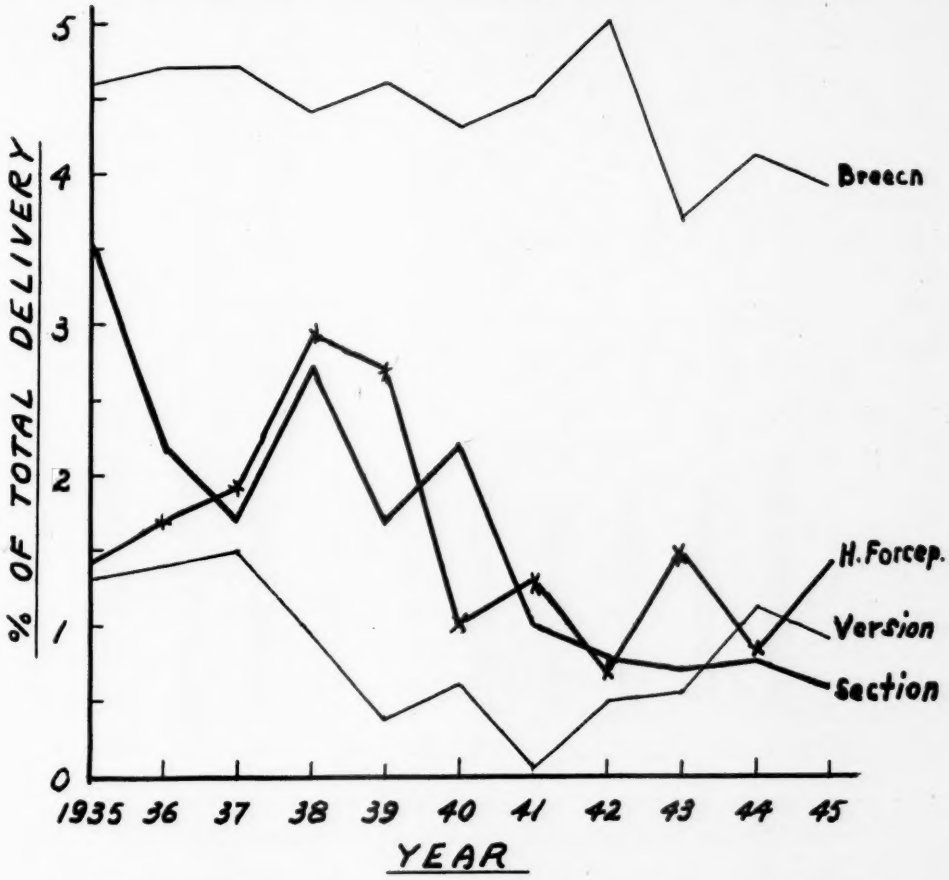

Fig. 2.—Relative incidence of breech, section, high forceps, and version delivery.

constitutes the smallest incidence that we have ever observed here, and it is much lower than the average incidence reported by other authors.[4, 6, 14] During the same period, almost all of the cesarean sections were performed by obstetricians. Cephalopelvic disproportion constituted the major indication. Central placenta previa and a very limited number of cases of toxemia and premature separation of placenta were also treated by cesarean section.

High forceps application which was included in the same ruling showed a similar decrease in utilization, as evidenced in Fig. 2.

Obstetricians' and General Practitioners' Work.—Of the total number of deliveries, 67 per cent were performed by general practitioners, and the re-

mainder by obstetricians.* It has been the policy of the Obstetrical Committee of this hospital to insure the ready availability of expert consultation for general practitioners and their patients at all times. As a result, a steadily increasing number of general practitioners' cases, especially the abnormal ones, have had the benefit of consultative advice from one or another member of the obstetric staff. Deaths, fetal or maternal, which occurred in cases in which the consultation of an obstetric specialist had been obtained, were included in the mortality figures of the latter group.

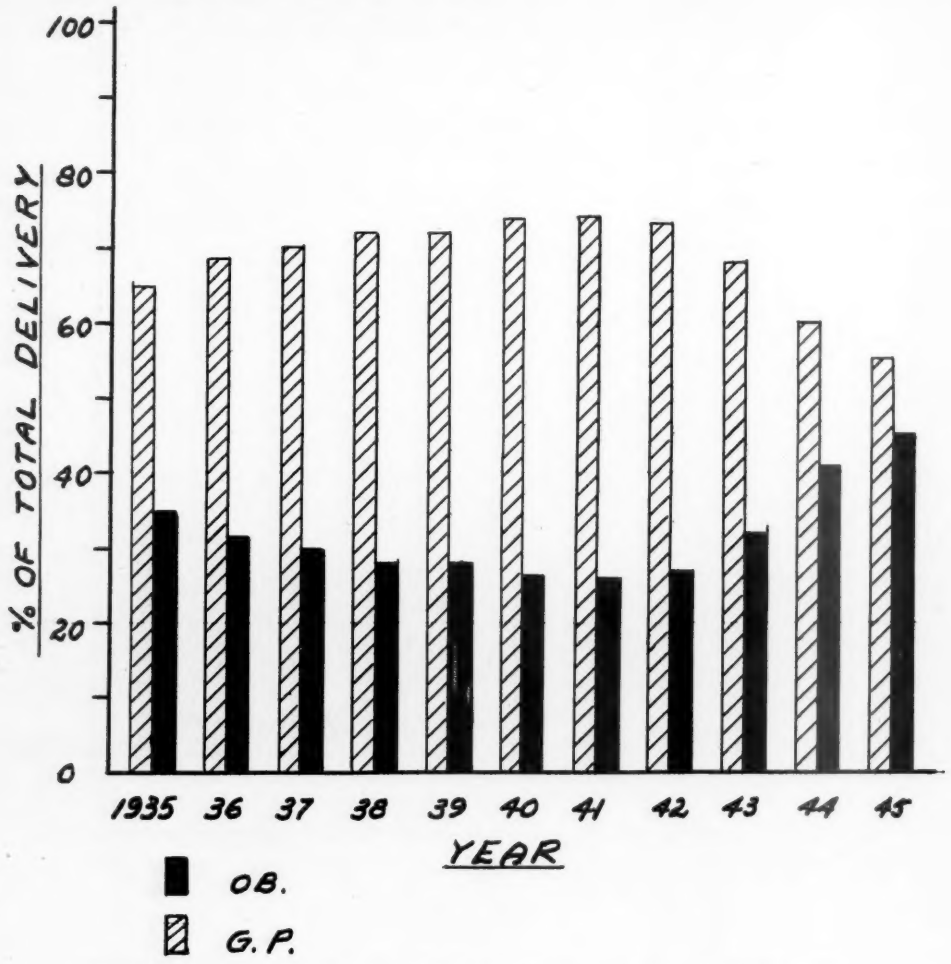

Fig. 3.—Annual variation of obstetricians' and general practitioners' work.

Fig. 3 shows that the percentage of deliveries performed by obstetricians has been steadily increasing in the last few years. It is possible that this was a contributory factor in the decrease of maternal and fetal mortality in this hospital during the same period.

Fetal Mortality.—Of 15,088 deliveries, 2.68 per cent were stillborn, and 1.82 per cent were neonatal deaths, comprising a gross mortality rate of 4.50 per cent. However, if we exclude the instances of macerated fetuses and congenital abnormalities incompatible with life, the average corrected mortality

*In the former figures are also included the deliveries performed by residents and interns, even though they were supervised by members of the obstetric staff.

would be 3.5 per cent. This incidence is high compared to 2.14 per cent reported by De Lee and Greenhill[2]; 2.67 per cent by Stander[3]; and 2.63 per cent by Beck.[9] It could be, however, favorably compared to 4.0 and 4.50 per cent, which is the average incidence occurring in all the hospitals of Illinois,[6] Ohio,[12] and a collected series from hospitals in Chicago.[6-8]

Fig. 4 shows the annual variation of both gross and corrected mortality rates. During the last four years there was a slight improvement in the fetal mortality. These figures confirm Stander's[3] contention that, despite the increasing number of hospital births and of mothers receiving prenatal care, the fetal mortality remains disappointingly high.

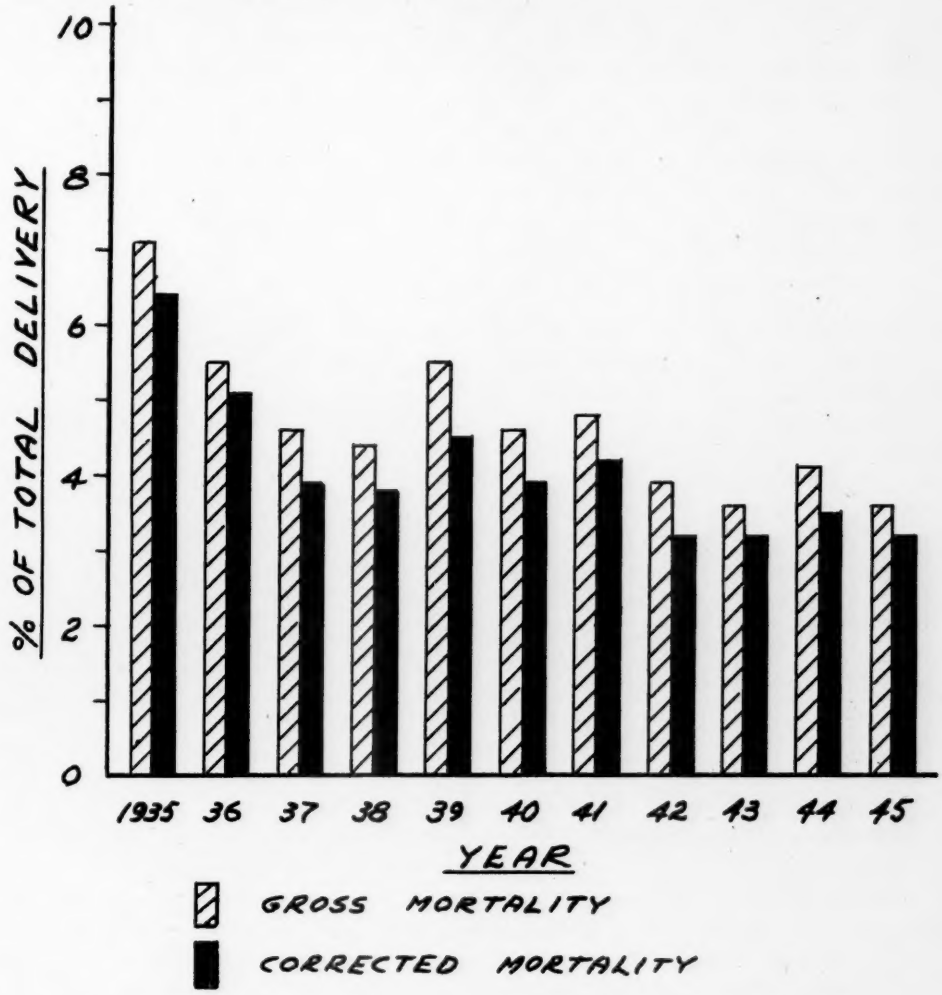

Fig. 4.—Annual infant mortality rates (includes stillborn and neonatal death).

Table II shows the gross infantile mortality relative to each type of delivery. The lowest incidence of fetal death occurred in forceps delivery; 1.66 per cent of the stillborn and 1.12 per cent of the neonatal deaths were the over-all mortality for the three major types of forceps applications. Of these, one-third occurred in high forceps and another one-third in midforceps. If, of the remainder, the cases of macerated fetuses and congenital abnormalities were excluded, then low forceps delivery would have an insignificant

TABLE II. FETAL DEATHS

TYPE OF DELIVERY	TOTAL DELIVERY	STILLBORN		NEONATAL DEATH	
		DEATHS	PER CENT	DEATHS	PER CENT
Normal	9,825	215	2.19	159	1.62
Forceps	4,282	71	1.66	48	1.12
Breech	656	73	11.10	41	6.24
Version	120	30	25.00	14	13.70
Section	205	13	6.34	13	6.34
Total	15,088	402	2.68	275	1.82

mortality rate. Although these figures are in disagreement with those reported by Irving,[14] we feel justified in minimizing the use of high and mid-forceps, but retaining the use of low forceps as a method of choice.

Breech and internal version delivery had the highest mortality rate. The uncorrected mortality for breech delivery was 17.35 per cent. Although high, it can be compared favorably with figures reported in other series.[8] Dieckmann,[13] in a very careful analysis of breech mortality, stated that it ranges from 3.8 per cent to 52 per cent. His own uncorrected mortality of 7.7 per cent is a proof of real improvement in breech delivery.

The management of breech presentation and its major problems have been outlined by Dieckmann.[13] It is our belief that this presentation should always be considered, particularly by the general practitioners, as a potential danger to the child, and any improvement in its handling will certainly reduce the fetal mortality.

The elevated mortality rate of internal version is a clear indication that its use should be relegated to the experienced obstetrician and then only in carefully selected cases.

TABLE III. FETAL DEATH RELATIVE TO OBSTETRICIAN AND GENERAL PRACTITIONER

TYPE OF DELIVERY	STILLBORN				NEONATAL DEATH			
	GENERAL PRACTITIONER		OBSTETRICIAN		GENERAL PRACTITIONER		OBSTETRICIAN	
	DEATH	PER CENT	DEATH	PER CENT	DEATH	PER CENT	DEATH	PER CENT
Normal	168	41.80	47	11.70	127	46.20	32	11.60
Forceps	48	11.92	23	5.90	28	10.15	20	7.26
Breech	47	11.60	26	6.40	25	9.10	16	5.82
Version	16	3.97	14	3.48	8	2.90	6	2.25
Section	7	1.74	6	1.49	12	4.36	1	0.36
Total	286	71.03	116	28.97	200	72.71	75	27.29

Table III shows the comparative fetal death rate relative to obstetricians and general practitioners. Of the total fetal deaths, 72 per cent were attributed to general practitioners, and the remaining 28 per cent to obstetricians. On the other hand, it should be emphasized that obstetricians managed more complicated cases and were called in consultation only after difficulties had arisen. Nevertheless, if we take into consideration the relative proportion of the total number of deliveries performed by general practitioners and that performed by obstetricians, it is quite evident that the highest incidence of infant loss occurred in the hands of the former group.

Premature Infant Mortality.—The criteria which have been adopted by several authors,[7-9] in studying premature infant mortality, are based on the weight and length of the baby. Unfortunately, we were not able to utilize this method since the weight and length of a large number of stillborn infants were

not recorded. Thus, our figures are based on the presumed length of gestation as determined by the attending physician or by the history taken by the house staff.

Fig. 5 shows the premature mortality rate for a five-year period from 1941 to 1945. Of the 146 premature (six to eight months' gestation) babies, almost 75 per cent died. This tremendous mortality constitutes an indication of improper management of premature infants, and it presents a real challenge to both the obstetrician and the pediatrician.

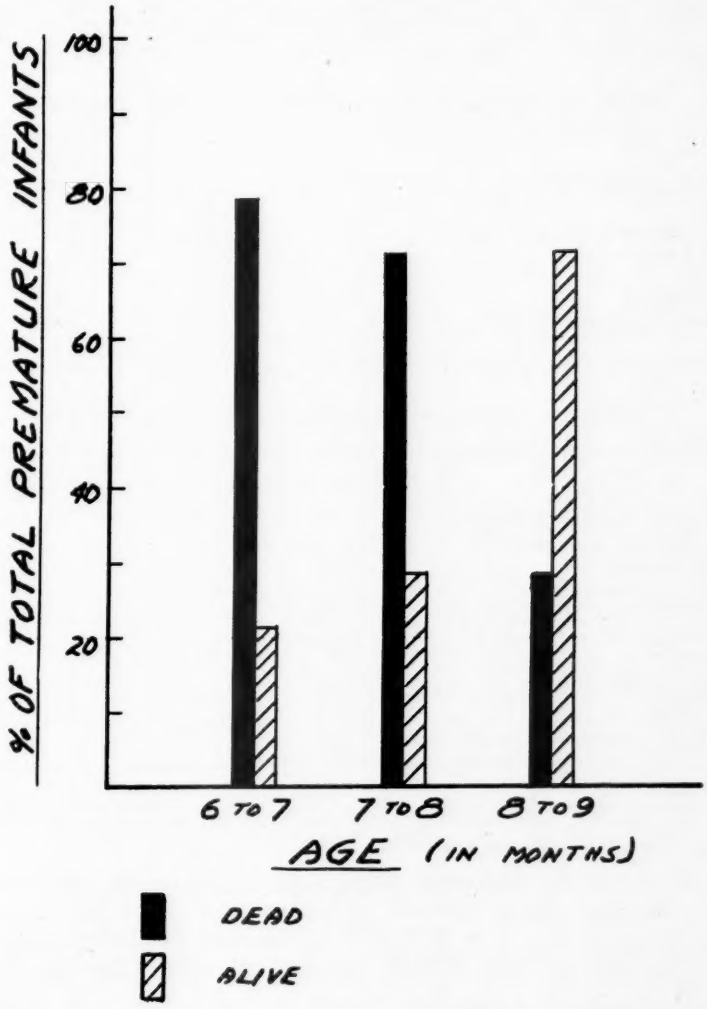

Fig. 5.—Premature infant mortality rates for five-year period from 1941 to 1945, inclusive.

The causes of prematurity and the methods by which the care of premature babies should be carried out have been fully discussed in papers elsewhere.[7-9] In this hospital, the highest incidence of prematurity was associated with breech presentation and toxemia. Whether breech presentation is the cause or the effect of premature labor is a subject of controversy.[11]

Causes of Infant Deaths.—The causes of infant mortality were arbitrarily classified as due to either fetal or maternal factors, although in some cases both factors were concerned.

TABLE IV. CAUSES OF INFANT DEATH; FETAL FACTORS

CLINICAL DIAGNOSES	STILLBORN		NEONATAL DEATH	
	NUMBER	PER CENT	NUMBER	PER CENT
Prematurity	128	31.82	134	49.50
Macerated fetus	64	15.88	0	0.00
Intracranial hemorrhage	30	7.46	29	10.70
Congenital abnormality	27	6.72	13	4.80
Atelectasis and pneumonia	26	6.48	39	14.30
Asphyxia	22	5.48	4	1.48
Unknown	105	26.16	52	19.22
Total	402	100.00	271	100.00

TABLE V. CAUSES OF INFANT DEATH; MATERNAL FACTORS

CLINICAL DIAGNOSES	STILLBORN		NEONATAL DEATH	
	NUMBER	PER CENT	NUMBER	PER CENT
Toxemia	36	8.90	6	2.21
Premature separation of placenta	30	7.50	1	0.37
Prolapse of cord	24	5.96	0	0.00
Placenta previa	11	2.80	7	2.58
Rupture of uterus	3	0.74	0	0.00
No evidence of maternal factor	298	74.10	257	94.84
Total	402	100.00	271	100.00

TABLE VI. CAUSES OF INFANT DEATH; AUTOPSY FINDINGS

CAUSE	CASES	
	NUMBER	PER CENT
Intracranial hemorrhage	20	19.80
Congenital abnormality	16	15.85
Atelectasis	12	11.90
Erythroblastosis	8	7.92
Craniotomy	6	5.90
Pneumonia	4	3.96
Asphyxia	3	2.97
Not determined	32	31.70
Total	101	100.00

Total deaths (stillborn and neonatal) = 673.
Total autopsy = 101, or 15 per cent of total deaths.

Table IV shows that among fetal factors prematurity was predominant, intracranial hemorrhage second.

Table V shows the maternal factors to which death could be attributed. The major maternal factor proved to be toxemia. The fact that in many of the deaths no evidence of a maternal factor was indicated does not exclude the possibility that one was indeed present. It simply had not been detected or recorded.

Autopsies were performed in 101 of the infant deaths (Table VI). Intracranial hemorrhage was the most frequent positive finding accounting for 20 per cent of the total. In 31 per cent of the autopsies no anatomic cause for death was demonstrated. Our autopsy findings are in close agreement with those of other authors.[1-8]

Maternal Mortality.—During the eleven-year period, 28 maternal deaths occurred, comprising a gross mortality rate of 0.18 per cent. However, from these, two cases can be excluded. The first was a 29-year-old patient, seven months pregnant, who was admitted to the hospital in severe shock following an accidental fall and died a few hours later. The autopsy revealed a trau-

matic rupture of the spleen and an aneurysm of the splenic artery. Because this death was not due to pregnancy, it seems reasonable to exclude it. The second case was a 41-year-old patient who was delivered at home and was brought to the hospital in severe shock. She died on the day of entry as a result of multiple lacerations of the vagina with internal and external hemorrhage. Since in our study, home deliveries were not included, this case is likewise deleted. Thus, the over-all maternal mortality was 0.17 per cent, or 1.7 per thousand deliveries.

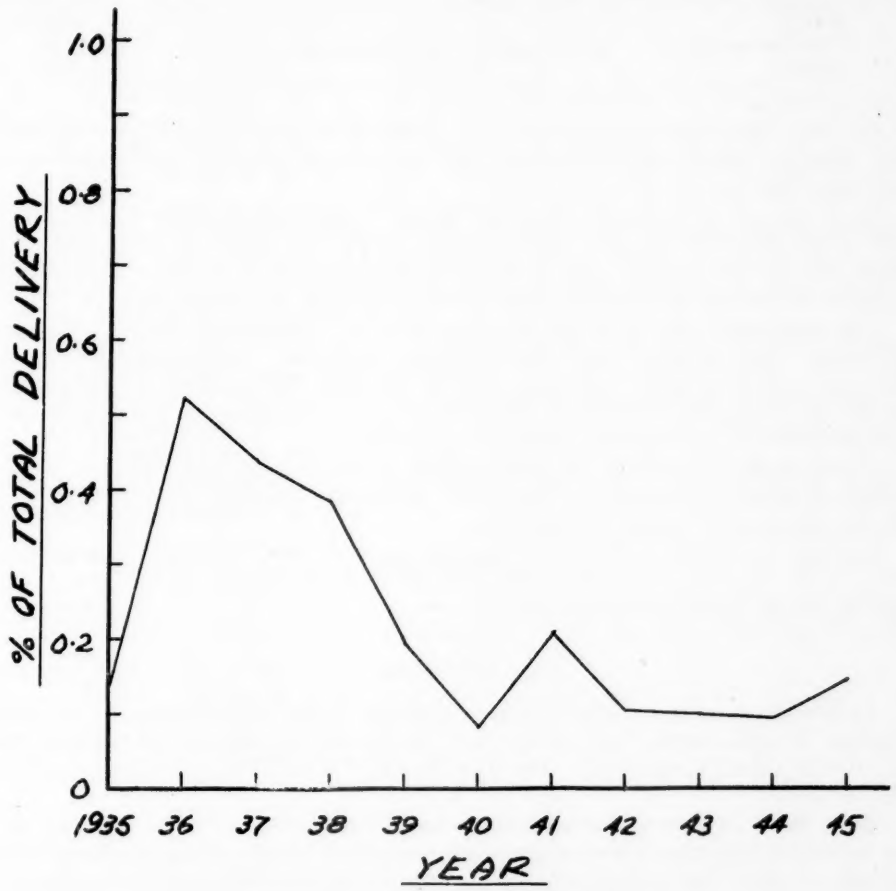

Fig. 6.—Annual maternal mortality rates.

Fig. 6 shows the annual maternal mortality rates. During the last four years it has ranged between 0.10 and 0.13 per cent, which represents considerable progress in the prevention of maternal death. These figures compare favorably with the best results reported by other authors.[3-5-10] In this hospital, the lowered incidence of cesarean section was, undoubtedly, an important factor in the diminution of the maternal death rate, as evidenced by the close parallelism of both curves (Figs. 2 and 6).

Of the 26 cases of maternal death, 19 occurred in the care of general practitioners, and seven in the hands of obstetricians. In two cases included in the latter group, the obstetrician was actually a delayed consultant.

Table VII shows the maternal death rate in conjunction with the type of delivery. Cesarean section had the highest mortality rate, being almost 3 per

cent. Although recent papers[4-14] report lower figures for section mortality, it is still generally agreed that this method of delivery is most detrimental to the mother.

TABLE VII. MATERNAL MORTALITY RELATIVE TO TYPE OF DELIVERY

TYPE OF DELIVERY	NUMBER OF CASES	DEATHS	
		NUMBER	PER CENT
Normal	9,825	6	0.061
Forceps	4,282	5	0.117
Breech	656	2	0.305
Cesarean section	205	6	2.920
Version	120	2	1.670

Of the total maternal deaths, six cases died before delivery. In two of these, postmortem cesarean section was performed in an unsuccessful attempt to salvage the fetus.

Hemorrhage and shock were the major causes responsible for 28 per cent of the total maternal deaths. Infection caused 25 per cent, toxemia and cardiac disease 18 per cent each, and pulmonary embolism 7 per cent. These figures are more or less in agreement with those reported by other authors.[5-6-10]

The patients who died of infection had the following clinical diagnoses: peritonitis—one patient; pneumonia—two patients; pyelonephritis—one patient; thrombophlebitis—one patient. It is noteworthy that puerperal sepsis was not a prominent factor. There was only one case of peritonitis which could be directly attributed to puerperal sepsis.

The patients who died of hemorrhage and shock were: rupture of uterus —three patients; placenta previa—two patients; possible uterine atony—one patient; rupture of vagina—1 patient.

Among the total deaths, necropsies were carried out in 15 instances, or 54 per cent. Signs of toxemia and cardiac lesions, mostly of rheumatic origin, were the major postmortem findings.

Comment

In order to have a better understanding of the significance of the figures reported in this paper, it is necessary to divide the eleven years comprising this survey into two periods: the first from 1935 to 1940, and the second from 1940 to 1945.

It is evident that deliveries by general practitioners predominated in the first period. This period was also characterized by abuse of cesarean section, the use of high forceps, and lack of control of the obstetric procedures. In consequence, a high fetal and maternal death rate was noted.

Although obstetricians continued to deliver a relatively small proportion of the cases at the outset of the second period, significant modifications in policy occurred. Rigid rules were established by the Obstetrical Committee regarding the performance of cesarean section and the use of the high forceps. Frequent utilization of obstetric consultants was required, and supervision of the delivery was instituted. These changes brought about definite improvements in standards of practice, with consequent decrease in maternal and fetal mortality. The improvement has been increasingly evident in the latter years of this period.

In the hands of the obstetric staff, breech delivery has received particular attention in recent years. Increasing emphasis on external version and careful roentgenologic study in cases of breech presentation have made possible accurate determination of cephalopelvic disproportion with consequent reduction

in the number of unnecessary cesarean sections. In addition, the use of the bag for dilatation of the cervix and routine episiotomy have made breech delivery less traumatizing.

Despite the continued efforts of obstetricians and pediatricians, little has, as yet, been accomplished in the reduction of mortality attributable to prematurity. It is our hope that by the more extensive employment of the procedures and principles noted concerning breech delivery, plus more circumspect use of maternal sedation, constant use of pediatric consultation and improved management of toxemia, the mortality among premature infants will be reduced.

Summary and Conclusion

1. Fifteen thousand eighty-eight deliveries observed during an eleven-year period have been analyzed (1935-1945).

2. For the entire period, the gross fetal mortality was 4.5 per cent, and the corrected mortality 3.5 per cent. Although it has been improved in the more recent years, these figures still remain high.

3. Breech and version delivery resulted in the highest and low forceps delivery in the lowest fetal mortality rate.

4. Fetal and maternal mortality were higher in the hands of general practitioners than in those of obstetricians.

5. Prematurity was the major fetal contributing factor and toxemia the major maternal factor causing fetal death.

6. The gross maternal mortality was 0.18 per cent, the corrected 0.17 per cent. It has been steadily improved throughout the past few years, during which time it has ranged between 0.10 and 0.13 per cent.

7. Hemorrhage and shock, infection, toxemia, and heart disease were the major causes of maternal deaths.

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A GRAPHIC METHOD OF PROGNOSIS FOR THE INFANT IN THE ANTENATAL CARE OF Rh-ISOIMMUNIZED PREGNANT WOMEN

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BECAUSE of the increased attention to the problem of Rh-isoimmunization in the antenatal care of pregnant women which has generally arisen during the last few years, a method of estimating the prognosis to the fetus, in any one pregnancy, of such women has been sought in this clinic. An extention of this would also apply to subsequent pregnancies.

An analysis of all the cases, 4,569, referred to our Rh laboratory service during 1946 for women whose expected date of delivery was some time in that year, was undertaken, and it was found that when the mother's Rh antibody titer, both agglutinating and blocking,[1] was serially plotted against the weeks of pregnancy, that the graphs fell into five well-defined curves, each an extention of the other. From the results observed of the condition of the babies born to these mothers, together with their subsequent immediate neonatal histories, it became apparent that for each grade of immunization charted the condition of the infants was relatively constant. It is on these results that we feel an accurate forecast can be made of the condition in which the child will be found when born.

Methods Employed

It is now the rule in our Obstetrical Clinics that, when a mother presents herself first for antenatal care, a routine Rh determination is done, after a careful history of previous pregnancies with their outcome, and also of previous transfusions, if any. This serves to eliminate the Rh-positive patients.

If the mother's reading proves to be negative, a few drops of her serum is incubated in a small test tube for an hour with two drops of known Rh-positive cell suspension, against a control. After centrifuging, the serum is decanted and two drops of beef albumin added, and again incubated for one hour.[2] The results are read as before. In the event of this reading being negative, a note recording that the patient is Rh negative but not yet immunized is made on her antenatal chart, and on each subsequent visit when blood is withdrawn for routine hemoglobin estimation a venous blood sample is set aside and the beef albumin test, outlined above, is repeated. Our usual practice is to see each patient every four weeks during the first trimester, then every three and two weeks during the second and third trimesters, respectively.

However, if at the time of first seeing the patient or at subsequent consultations, the beef albumin test gives a positive agglutination reading, indicating a degree of isoimmunization, a test tube titer is set up using the

patient's serum and known Rh-positive cells of various subtypes. Where possible, the husband's blood is also used for this test. The cells are first used in saline suspension in order to demonstrate free agglutinating antibodies; beef albumin being then used to bring out the blocking antibodies. Both these titers are incubated for an hour and read under the low power of the microscope after sufficient centrifuging to pack the cells at the bottom of the tube.

This titer result for agglutinating and blocking antibodies is then charted as shown in Figs. 1 to 5, and the progress of the pregnancy watched carefully by subsequent plotting of titers. The patient may be asked to return for more frequent estimation than is indicated in Figs. 1 to 5 if thought necessary.

Whenever it is possible to obtain a sample of the husband's blood, Rh subgrouping tests are done with a view to detecting whether, if positive, he is homo- or heterozygous. Often with multiple pregnancies and living children it is possible to obtain corroborative evidence of this from Rh testing of the family.

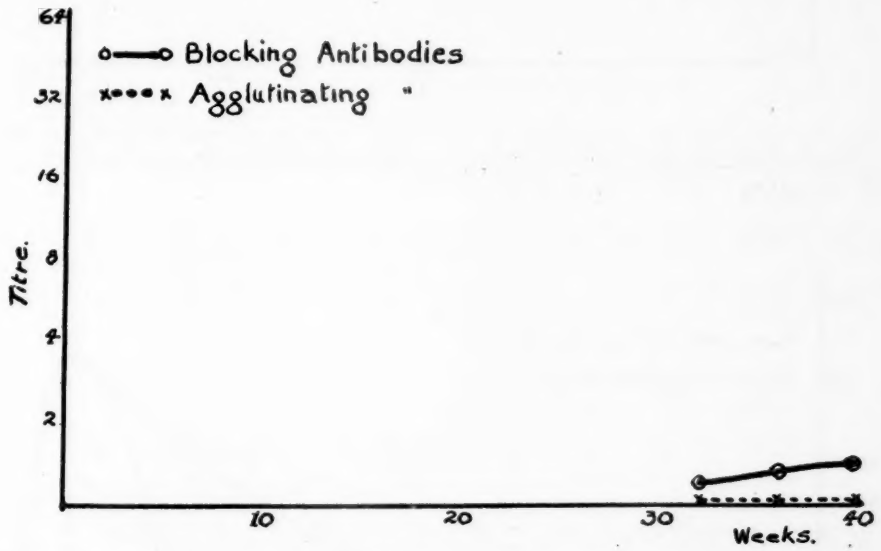

Fig. 1.—Grade I; shows only very slight immunization in later weeks of pregnancy. Babies do well even without treatment in the immediate postnatal period.

Laboratory Results

In the laboratory service attached to the Montreal Maternity Hospital 4,569 preliminary estimations of Rh were done during 1946. Of these, 1,609 were discounted from the results used in this investigation because they were private cases referred to the laboratory and they showed evidence of selection. However, graphs have been prepared of these private cases which showed isoimmunization to be used as a check on the results obtained with the public cases. They have been found to bear out the findings so obtained.

In the 2,960 clinic cases examined as a routine, 391 were found to be Rh negative, giving a percentage of 13.2 per cent. For this report we have not broken down those negative patients who showed signs of isoimmunization into categories showing numbers of pregnancies, but have simply recorded the total number found to be immunized. These are 33, or 8.45 per cent, of the Rh-negative cases or 1.12 per cent of the whole.

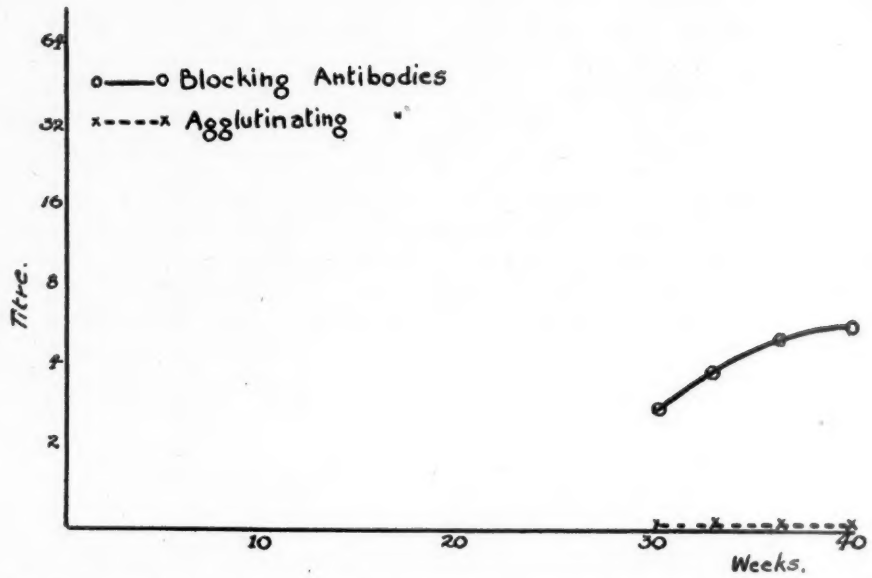

Fig. 2.—Grade II; late appearance of antibodies. Rise in blocking antibodies in the last few weeks of pregnancy not above dilution 1:8. These babies are born at term showing some clinical signs of erythroblastosis of moderate severity. Blood picture at birth confirms this. Infants are usually easily saved by transfusion, etc.

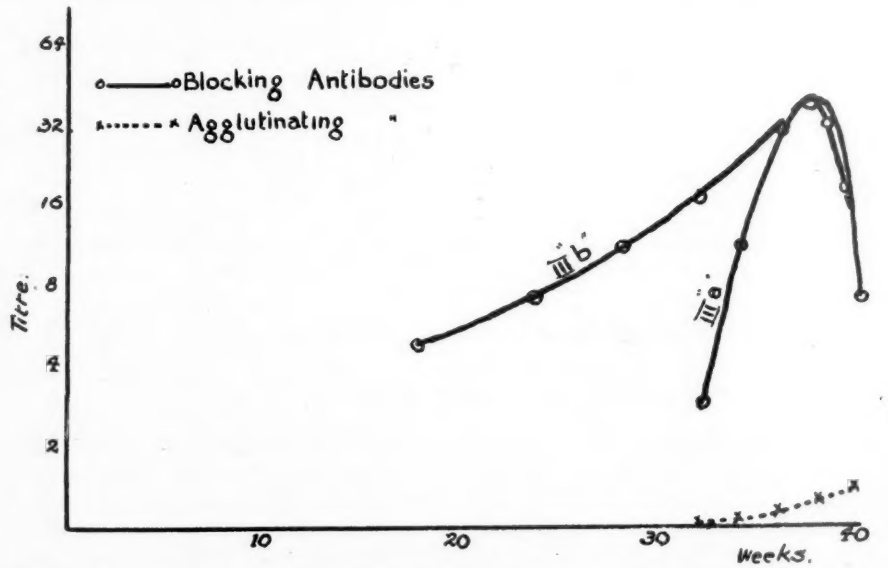

Fig. 3.—Grade III a; a sharp rise in blocking antibodies to dilution 1:32 with often a sudden drop in the last two weeks. Babies severely damaged. May be salvaged by prompt action immediately after birth.

Grade III b; antibodies demonstrable relatively early in pregnancy rising to 1:32 with sometimes a sharp drop in the last two weeks. Prognosis very poor for the baby. Term babies often deadborn.

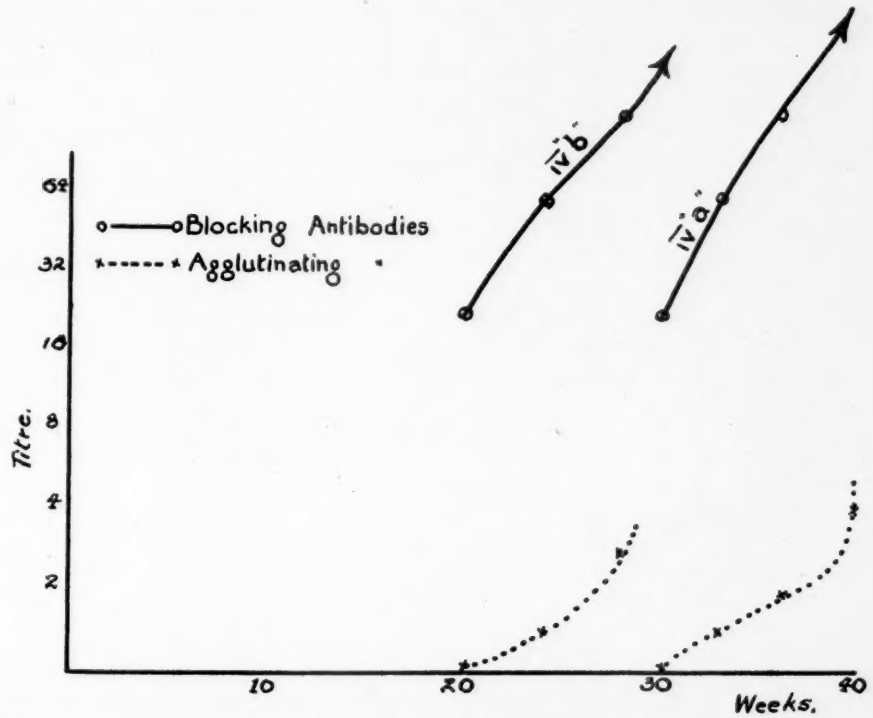

Fig. 4.—Grade IV a; a very sharp rise in the later months to, and above, dilution 1:64 with some agglutinating antibodies. Prognosis very poor for the baby, severe anaemia with oedema. Usually deadborn at term or a week or so before.,

Grade IV b; a shift to the left of the first appearance of antibodies in heavy concentration at, or about, the period of theoretical viability. Prognosis. Macerated dead fetus, premature by several weeks.

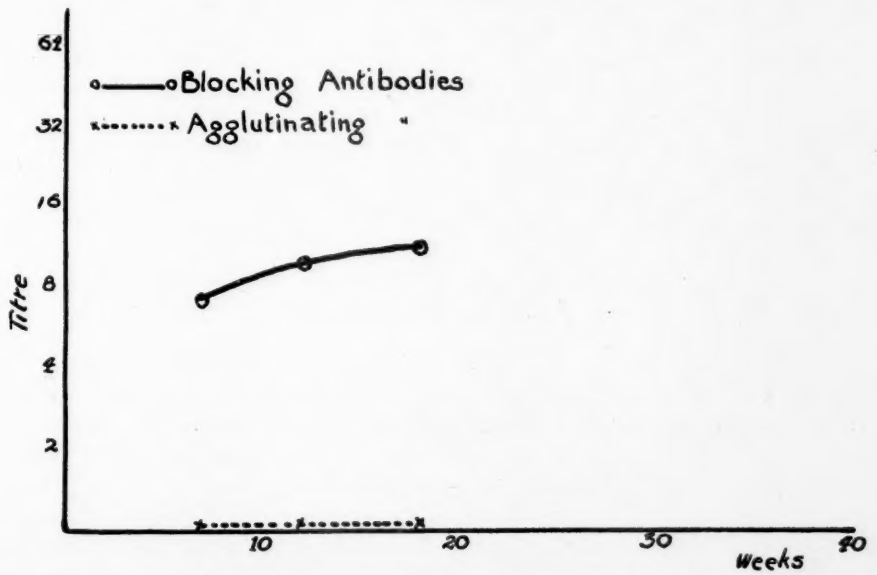

Fig. 5.—Grade V; the appearance of blocking antibodies (with sometimes agglutinating antibodies) in appreciable concentration, dilutions 1:4 and over before the twentieth week. Prognosis hopeless with an Rh-positive baby. Result is abortion or early miscarriage. Future prognosis with a homozygous Rh-positive husband is likely to be uniformly disappointing.

In each case the diagnosis of erythroblastosis fetalis was confirmed in the child either by autopsy or by blood studies in the children who survived. Also it was proved in all the cases submitted that the children were Rh positive, and in each case where material was available, it was shown that the child's red cells were sensitized and liable to breakdown to a greater or lesser extent by circulating antibody in the mother's serum.

Discussion of Curves

Taken generally the curves show that the later in pregnancy antibodies are demonstrated, taken with a low titer, the better the prognosis, as was expected from previous clinical impressions. Within the compass of the time scale, i.e., up to delivery, the only curves which have tended to show a drop in the later weeks are those in Grade III. This drop has been noted by other observers and its adverse affect on the baby commented on. From our series it was not possible to determine whether the maximum damage to the baby was started at the peak of the curve or during the descent. It has been postulated that the drop in titer of the mother's antibody was an indication of increased absorption of antibody by the fetus. Attractive as this simple hypothesis is, more requires to be known of the protective mechanism, which the fetus has for dealing with a flood of antibodies, as it will be appreciated that a drop in titer from say 1:32 dilution to 1:8 indicates a considerable absolute quantitative drop. This decrease, if it all passed to the fetus in one or two weeks, would surely overwhelm it, and yet some of these babies are born alive in sufficiently good general condition to be salvaged. Every case studied in Grade III did not show this drop, but in these curves it was found as follow up that the drop occurred up to the two to three weeks post partum. Those in Grade IV did not show an appreciable decrease in titer for many weeks post partum. On examining the results for the babies it was found in Grade III that the babies had a better chance of survival if the drop in titer occurred in the postpartum period, which bears out our findings that any shift to the left in any one grade makes the prognosis proportionately worse. One fact emerges and that is the lateness which antibodies are often first demonstrated, as an average, usually about the thirty to thirty-second week. This shows that great care is required in the later weeks to keep a close check on the patient's titer as she comes to term. We regard the appearance of agglutinating antibodies in rising titer as also shadowing the prognosis. When considering the application of the curves to any one case it should be borne in mind that each grade shown is an average curve and deviation from the average should be expected. However it has been found easy to make an accurate forecast by interpolation using the curves and the basic principles outlined; particularly when the patient's history is taken into account. A better baby can be expected if the patient has had no suspicious history in previous pregnancies.

The series given being that of one year's work in the public service of this hospital, is, of necessity, rather limited. Notwithstanding this the results claimed have been amply borne out by checking against the available records for past years and from the private records of our consultant staff who have kindly lent them for this purpose.

One apparent exception to the suggested scheme given above has occurred, and that was in the case of an Rh-negative mother who had previously given birth to an erythroblastotic child. During the pregnancy under review she showed demonstrable blocking antibodies to a titer of 1:4 between the tenth and eighteenth weeks. These then disappeared and she delivered a normal child who was Rh negative. The husband is heterozygous.

Practical Use of the Curves

The usefulness of being able to give a prognosis for the fetus along general lines is apparent. In some cases it may be considered advisable to terminate the pregnancy a few weeks before term by cesarean section with a view to saving the fetus from excessive breakdown of its cells. A study of the curves shows that in cases which fall into Grades I and II this may be justified. However when the titration curves approximate to Grade IIIb and IV, then it is questionable whether the increased risk to the mother is justified when the prognosis to the baby, even when a well-organized resuscitation team is at hand, is so poor.

It is felt that, for those patients who come under Grades IV and V, if the husband is homozygous positive, then further pregnancies should not be attempted.

In our cases in which antibodies are demonstrated during the antenatal period preparations are made as the woman is brought to hospital for delivery, to have a resuscitation team ready to take charge of the infant. This team, which consists of a "Transfusion Officer" and a Pediatrician, has at their disposal Rh-negative blood, cross matched against the mother and laboratory facilities on a 24-hour basis quickly to determine, from heparinized cord blood the infant's Hb, packed cell volume, icteric index, and the Rh of the blood, together with any evidence of sensitivity of the infant's red cells. On these findings the appropriate treatment for the infant is based.

Protection of the Fetal Liver

On the advice of one of us (N. W. P.) late in this series an effort was made to protect the fetal liver from excessive damage in cases of known isoimmunized pregnant women. The method used was to have the mother take adequate doses of Methionine by mouth from the time when antibodies were first demonstrated until she was delivered. The infant is also given Methionine by mouth during the immediate postnatal period. In a small series of six cases the results have been encouraging. Further work is proceeding and will be the subject of a further communication.

Summary

A graphic method for estimating the prognosis of the child in cases of isoimmunization against the Rh factor during the antenatal period is given.

The technical details are outlined.

Suggested uses for this method of prognosis are offered.

The taking of methionine by the mother is put forward as a method of protecting the fetal liver.

This work was made possible in part by a grant from the Baxter Laboratories, Inc., and also the brand of Methionine used in this investigation was Meonine manufactured by John Wyeth & Brother (Canada) Limited, Walkerville, Ont.

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CHARACTERISTICS OF THE NORMAL MENSTRUAL CYCLE*

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A NUMBER of critical studies[1-4] has shown that the lengths of apparently normal menstrual cycles vary widely, and that absolute regularity in the individual patient is exceptional. The results of some of these investigations are open to re-examination.

The majority of these studies lacks proof of the ovulatory nature of the cycles, i.e., whether true menstruation actually had occurred. In one study[5] the presence of midperiod pain was taken as the criterion of ovulation; this is suggestive but not conclusive evidence of ovulation or of adequate corpus luteum function. Several studies included many relatively young patients, and in one study all the postmenarchial periods of some patients were included. The data of these studies would include anovulatory cycles.

In none of the studies was any attempt made to eliminate patients with endocrine disturbances save those of sufficient magnitude to be obvious during the routine examinations of student nurses or of women in a contraception clinic. In one study[6] patients were sent a questionnaire and were followed by mail; the value of these data is questionable.

The existence of uterine factors was determined by pelvic examinations in one study.[7] No mention of routine pelvic examination is made in a study of student nurses.[3]

There are, finally, lesser factors which are known to influence the regularity of menstrual cycles, as minor illnesses, changes in environment, travel, or alterations of working hours (especially applicable to nurses). Although gross disturbance in function may have been eliminated in the selection of the final data,[3] there is no record that these supposedly minor factors were discounted.

The data of these studies provide interesting comparisons. Two of the curves of Fig. 1 are quite similar, but differ widely from the other three which show less variation in the cycle length. Both these curves were obtained from studies of student nurses, whereas the other three were based on heterogeneous groups.

Materials and Methods

Menstrual data collected in the Endocrine Division avoid many of the drawbacks of data previously reported by others; they appear to be ideally suited for the establishment of the true norms of menstruation.

During the course of routine sterility surveys[8] both members of the couple are studied intensively. The survey of the wife includes a complete and thorough

*Part of the expenses of these studies was defrayed by grants to one of us (E. C. H.) from the National Committee on Maternal Health, Duke University Research Council and Ayerst, McKenna and Harrison, Ltd.

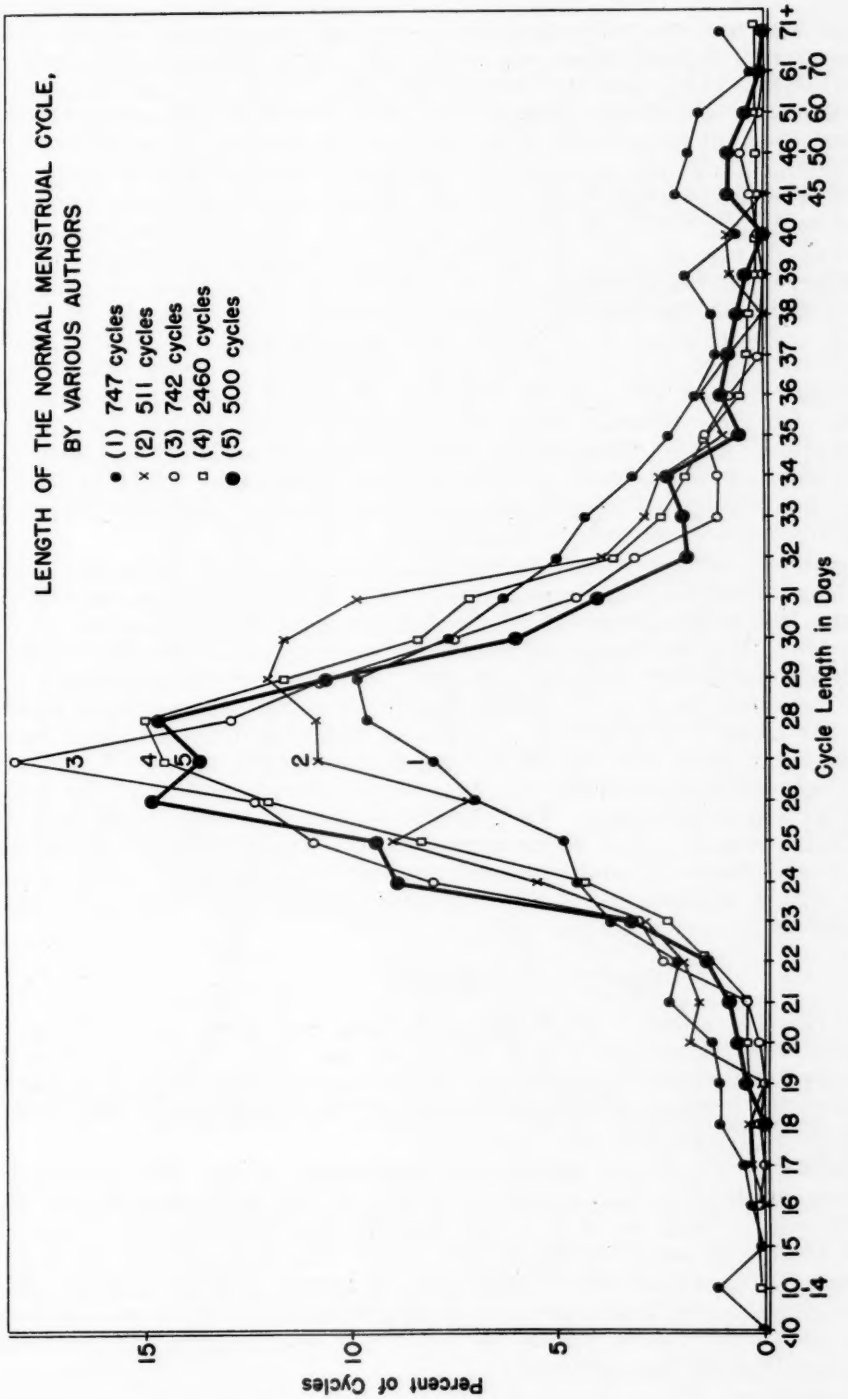

Fig. 1.—Graphic representation of the length of the normal menstrual cycle reported by various authors.

history and physical examination (with an emphasis on the gynecologic and endocrine aspects), basal metabolism tests, roentgen-ray examination of the sella turcica, routine urine and blood examinations, special blood chemistry studies when indicated, tubal tests with radiopaque oil, postcoital tests, endometrial biopsies at the onset of bleeding, and basal (rectal) temperature records. The importance of timing these studies with the menstrual cycle necessitates close and constant supervision of the patients for four to six months or longer.

For this study, 109 patients were selected. No more than 13 cycles of any patient were used: accordingly, no one patient contributed more than 2.5 per cent of the data. No patient with organic or functional ovarian disorders, endocrine disease, or with uterine factor as determined by history, pelvic examination, or uterosalpingography was included. No patient was less than 20 years of age. Six patients (5.5 per cent) were 20 to 24 years old, 34 (31.2 per cent) 25 to 29 years old, 43 (39.5 per cent) 30 to 34 years old, 22 (20.1 per cent) 35 to 39 years old, and 4 (3.6 per cent) were 40 to 42 years old. A total of 524 cycles of these 109 patients followed with basal temperature records, was studied. On these records, minor events as late hours, restless sleep, or travel were marked; febrile illnesses, of course, were immediately apparent; these records were excluded from our studies. The presence of intermenstrual spotting, or the omission of temperature recording for more than two to three days also eliminated some records from study.

Arbitrary criteria were established so that the basal temperature records could be analyzed in a uniform fashion. The *time of ovulation* was calculated from the last temperature before the beginning of the continuous (progestational) rise. The *average temperature rise* was estimated from the difference of the mean preovulatory and postovulatory temperatures. The *duration of temperature rise* was measured from the beginning of the progestational rise to the end of the phase of constant rise. Cycles in which no definite time of ovulation could be established from the basal temperature record, and which were nevertheless not definitely anovulatory, were termed *indeterminate cycles* and were treated as a separate group. The *duration of bleeding* included all days during which there was any show of menstrual blood. The criteria for estimating the presence and degree of progestational response in endometrial biopsy specimens (taken within eighteen hours after the onset of bleeding) were ones employed for many years on our service.

Results

Of the 524 recorded cycles 500, or 95.4 per cent, were ovulatory, 13, or 2.5 per cent, were anovulatory, and 11, or 2.1 per cent, were indeterminate, as judged by basal temperature records. All 58 biopsies from cycles with ovulatory rises revealed progestational endometriums, thus confirming the interpretation of the temperature curve.

Length of the Menstrual Cycle.—The length of the 500 menstrual (i.e., ovulatory) cycles is plotted as curve 5 in Fig. 1. No cycles shorter than 19 days were recorded. Only one cycle longer than 60 days was observed. Only 3.2 per cent of the cycles was 19 to 22 days in length, 21.4 per cent was 23 to 25 days in length, 53.6 per cent was 26 to 29 days in length, 17.8 per cent was 30 to 36 days in length, and 4 per cent was longer than this. *Thus, over half of the normal menstrual cycles* was 26 to 29 days in length, and 92.8 per cent fell within the 23 to 36 days interval.

Comparison of our curve with those of other workers reveals several interesting features. When anovulatory cycles are eliminated, the short ones (less than 19 days) apparently disappear from the curve. All the curves show an approximately equal and rather low incidence of cycles longer than 36 days.

There is no reason to believe, accordingly, that any significant percentage of the long cycles observed by others was anovulatory. Curves 1 and 2, which differ most, are based on a selected group (nursing staff) which is often under unusual environmental strains. It is also interesting to note that the figures of Haman[7] based on 2,450 cycles in mature women, attempting the "safe period" type of contraception, agree most closely with the frequency distribution observed in our patients. This may be explained by the greater maturity of his

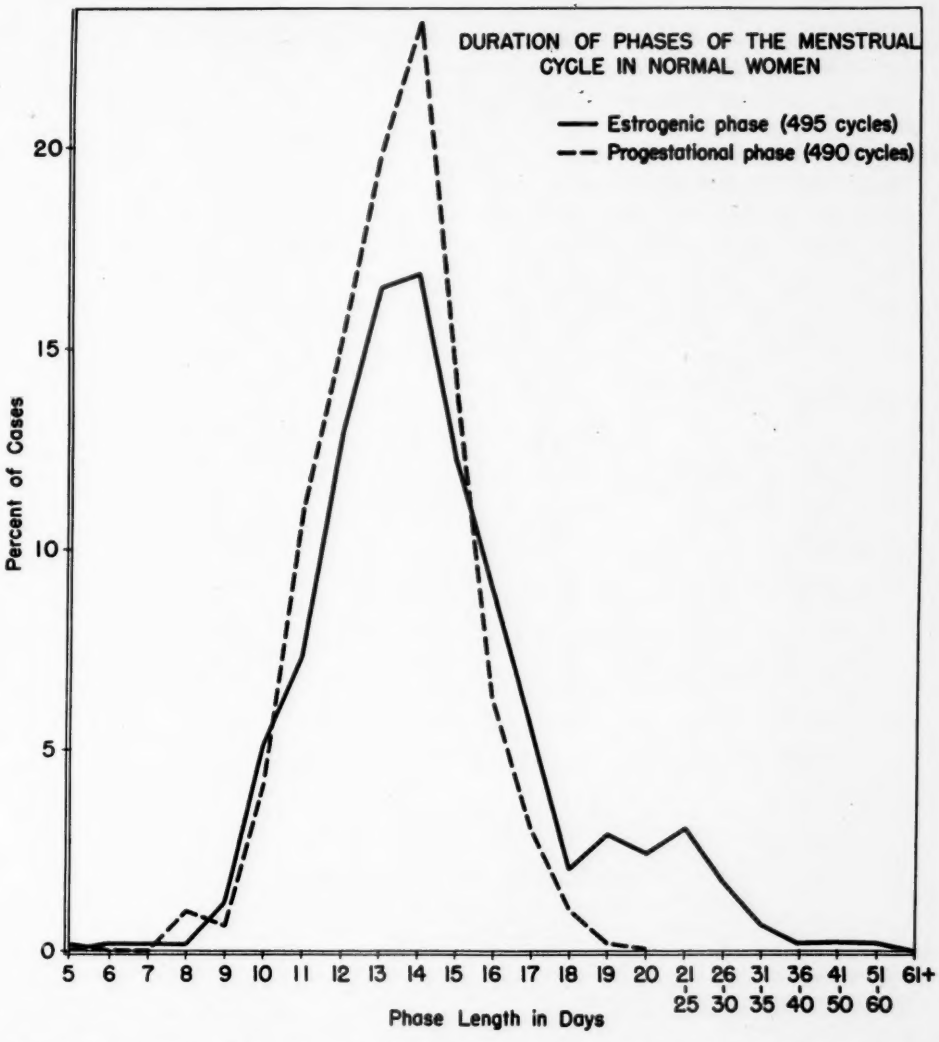

Fig. 2.—Graphic representation of the length of the phases of the menstrual cycle in normal women.

patients (with a lower incidence of anovulatory cycles), by the variety of environmental status, and by the sheer weight of numbers, which would tend to dilute out the minor factors.

The anovulatory cycles ranged from 16 to 38 days in length. Their relatively small number (a total of 13 cycles) makes any plotting of the frequency distribution valueless. There were 11 indeterminate cycles. These ranged from 15 to 37 days in length, and were also widely scattered across this range.

The Estrogenic Phase.—Fig. 2 shows the length of the estrogenic phase as measured in 495 ovulatory cycles. In the majority of women (79.6 per cent) this phase was 10 to 16 days in length. A small number (1.9 per cent) was less than 10 days in length, but a significant proportion was relatively long. The estrogenic phase was 17 to 25 days long in 15.6 per cent, and longer than 25 days in 2.9 per cent.

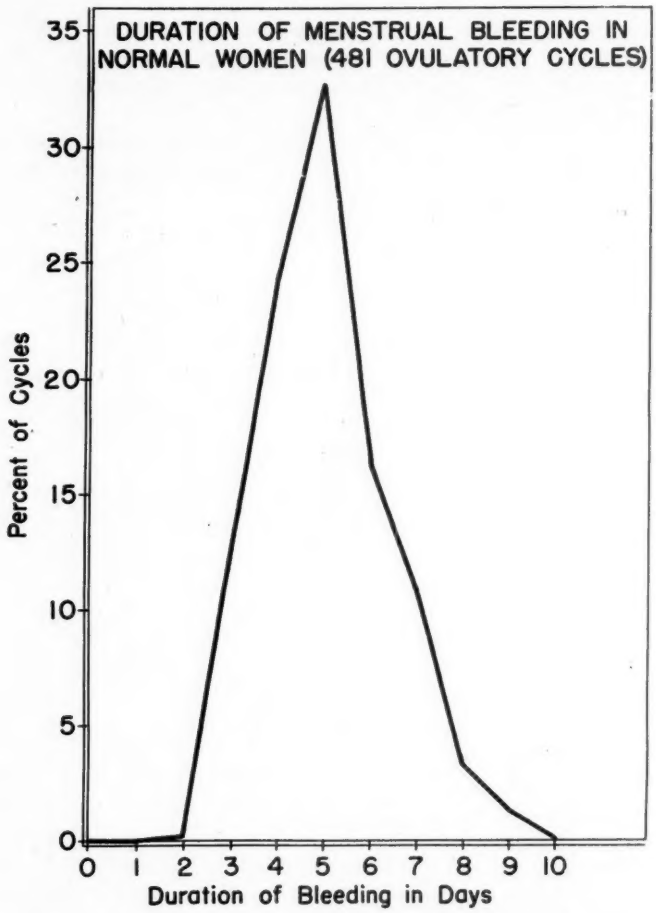

Fig. 3.—Graphic representation of the duration of bleeding in 481 ovulatory cycles in normal women.

The Progestational Phase.—Fig. 2 also shows the length of the progestational phase of 490 cycles. One progestational rise was only 5 days long. Otherwise, there was none shorter than 8 days or longer than 19 days. It is believed usually that the progestational phase is fairly constant, ranging from 11 to 14 days in length. In our material only 69.5 per cent of the cycles showed this duration. The progestational phase was 10 to 16 days in length in 94.0 per cent, less than 10 days in 1.8 per cent, and 17 to 19 days in length in 4.3 per cent.

These data agree with the belief that the unusual length of the ovulatory cycles results from a prolongation of the estrogenic phase. In nearly one-fifth of the cycles this phase was longer than 17 days. It is also interesting that a short estrogenic phase is unusual. The measurements of the progestational phase, however, do not confirm its supposed constancy; approximately two-thirds of

the cycles fell within the 11 to 14 days' range. It required a 7-day interval (10 to 16 days) to include most of the cycles. Both very short and very long phases, however, were rare. The progestational phase is more constant in length than the estrogenic phase.

Duration of Bleeding.—Data on the duration of bleeding were available in 481 cycles. The frequency distribution is shown in Fig. 3. In one cycle (0.2 per cent) bleeding was less than 3 days in length and in none was it longer than 9 days. In 95.4 per cent of patients, bleeding was 3 to 7 days in length; however, in more than two-thirds (68.4 per cent) of all the cycles, bleeding was 3 to 5 days in duration.

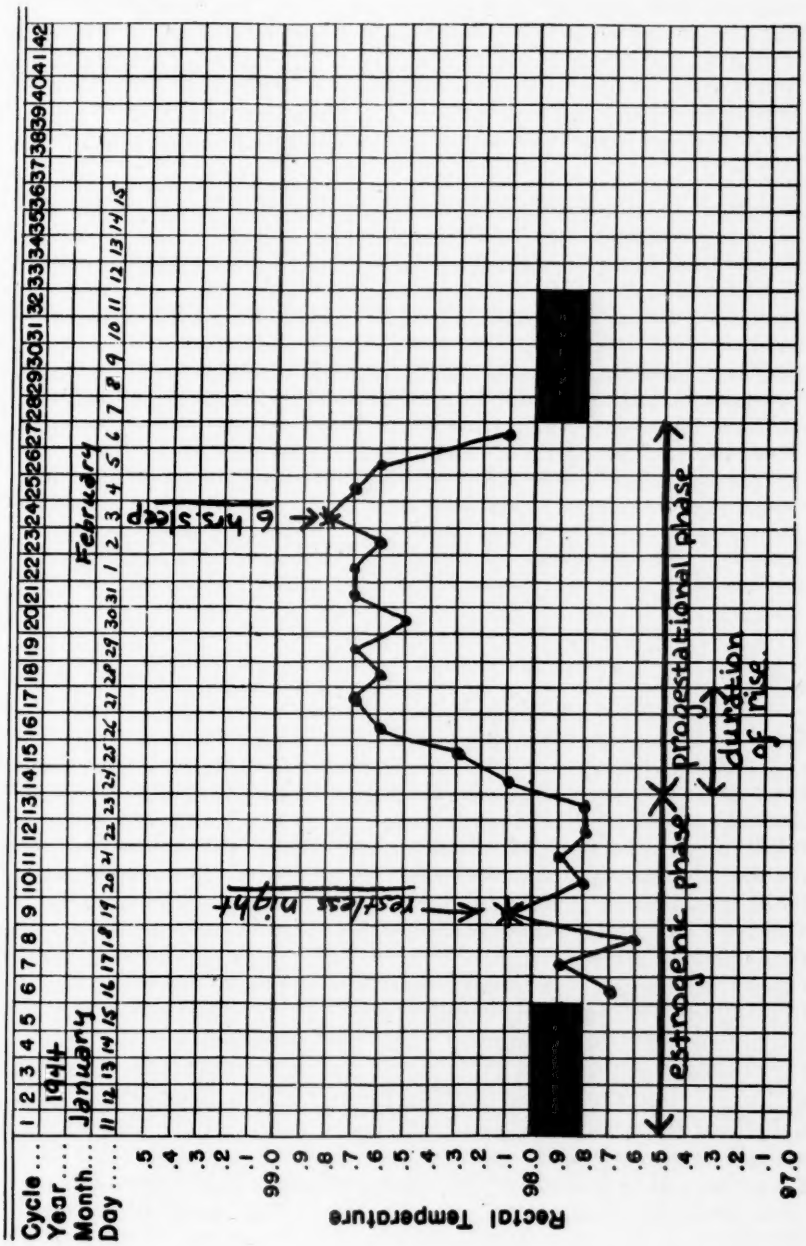

Fig. 4.—Typical basal temperature chart, showing the method of recording and evaluating the data.

No mention has been made of the actual amount of bleeding. Although this was recorded for most women, it was felt that the pad count and the patient's own estimate of the degree of pad saturation were far too individual to yield information of any real value. We have made, therefore, no attempt to draw conclusions from these data.

Basal Temperature Records.—The difference in the mean temperatures of the pre- and postovulatory phases was estimated in 486 cycles. In a small number (11.3 per cent) this difference was relatively small (0.2 to 0.5° F.). The rise usually was 0.6 to 0.9° F. (78.9 per cent). In 9.8 per cent of the cycles the temperature rise was 1° F. or more. The greatest rise observed was 2.0° F. in two cycles of the same patient (0.4 per cent). This range emphasizes the value of recording the temperatures in degrees Fahrenheit and on a relatively large scale, as shown in the sample chart (Fig. 4). The use of a smaller scale or of degrees Centrigrade makes the recognition of a significant number (11.3 per cent) of ovulatory cycles very difficult. It is possible also that a greater variability in oral temperatures may conceal a considerable proportion of truly ovulatory cycles.

The duration of the postovulatory rise is of interest. This was estimated with reasonable accuracy in 459 cycles. In 13.7 per cent the temperature rose sharply and leveled after one day. In 69.3 per cent the rise continued sharply for one to four days, and then leveled. In the remaining 30.7 per cent the rise was more constant and gradual, extending over a period of five to nine days. In a small number of cycles,[11] not included in these figures, there were signs of a very gradual, lowgrade temperature rise, neither conclusively ovulatory in character nor definitely anovulatory. Unfortunately, no bleeding biopsies at the end of these 11 cycles were available. These were "indeterminate" cycles and they have been excluded from the statistical calculations.

At the present time we have no idea of the significance of the slope of the progestational rise. Whether this reflects the degree of corpus luteum activity, whether it is purely an individual response, or perhaps a combination of these and other factors is a matter of conjecture. Our studies do not yield new information of the exact correlation of ovulation and the basal temperature rise. It is known that a characteristic temperature rise may be produced in the castrate by the injection of progesterone.[9] We have accepted this rise, therefore, as presumptive evidence of ovulation. Whether the observed temperature rise is entirely a progesterone reaction phenomenon, whether the actual process of ovulation plays a role, and how soon after actual ovulation the basal temperature is affected are not known. Therefore, our estimates of the time of ovulation are probably later (it may be by as much as two to three days in some cycles) than the actual ovulation.

Correlation of Endometrial Biopsies and Basal Temperature Records.—A total of 61 bleeding biopsies following a recorded cycle was available for study; 58 of these were from ovulatory cycles, and 3 were from anovulatory cycles, as judged by basal temperature records. *All 58 biopsies after ovulational temperature curves showed histologic evidence of progestational change.* In 86.3 per cent (50 biopsies) histologic and temperature length of the progestational phase agreed within forty-eight hours. In two instances (3.5 per cent) histologic change was less advanced than the duration of the progestational temperature elevation indicated (i.e., there was more than two days' difference in the readings). In six cycles (10.2 per cent) the progestational change was advanced further than was expected from the duration of the temperature elevation. In these eight cycles the curves did not show any unusually high or low temperature rise. It is not clear, therefore, whether this discrepancy is due to error in our method of estimation or whether it may possibly indicate quantitative differences in corpus luteum activity which are not shown by the basal

temperature record. From the point of view of fertility, only two biopsies yielded information significantly different from that obtained from the temperature records; this satisfactory correlation may eliminate the necessity of performing endometrial biopsies in many patients.

Three biopsies were obtained after cycles judged anovulatory from the temperature record. Two of these showed late estrogenic endometriums, compatible with the length of the cycle. The third biopsy showed full-blown progestational changes despite a flat temperature curve. If this temperature record is accurate, and we have no reason to doubt it, no explanation for the discrepancy is apparent.

Summary and Conclusions

For many years the paradoxical statement of Fraenkel that "the only regular feature of menstruation is its irregularity" has been repeated in the literature. These statistics indicate that most features of truly normal menstruation are fairly constant and do not vary more widely than other physiologic functions. There is no doubt that menstruation, as the final common manifestation of highly complex neural and hormonal influences, is a delicate indicator of disturbances in these fields. This, however, does not justify the statement that true (ovulatory) menstruation is an unpredictable, erratic phenomenon.

The menstrual cycles of 109 carefully investigated, healthy adult women were studied by means of basal temperature records and endometrial biopsies at the onset of bleeding. A total of 524 cycles, presumably free of the influence of unusual stresses, forms the basis of this report. These cycles were analyzed statistically for cycle length, duration of the estrogenic and progestational phases, duration of menstrual bleeding, characteristics of the basal temperature rise, and correlation of temperature curve and endometrial biopsy.

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RELATIONSHIP BETWEEN CERVICAL MUCUS AND BASAL TEMPERATURE CYCLES*

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CYCLIC variations in some of the physical properties of cervical mucus of normal women are well recognized. The amount of mucus is greatly increased during the ovulatory phase of the menstrual cycle, and at this same time a marked decrease in the viscosity and in the cellularity of the mucus is noted.[1-7] Spermatozoa can penetrate the mucus to an appreciable distance only during this period of the cycle and during menstruation.[1-4, 7, 8] These changes in the cervical mucus have been shown to be under hormonal influence[4, 9-11] and coincide with the time of ovulation.

Another method for estimating the approximate time of ovulation is based on the fact that at this time the basal temperature shifts from a lower to a higher level. Reviews of the literature on this subject are given by Barton,[12] Pommerenke,[13] and Tompkins.[14]

Barton and Wiesner[15] observed in their studies of fertile women that the cervical mucus cycle bears a definite time relationship to the basal temperature cycle. According to these workers the mucus increases in amount and becomes transparent and acellular just before the temperature shift. After one to three days it decreases in quantity and again becomes cellular. In previous communications the present authors also showed that the temperature shift occurs during the time of increased mucus production in midcycle.[5, 7] These results were based on a relatively small series of cycles on relatively few subjects. Many additional observations on a larger group of subjects have now confirmed this finding and have also made possible a better understanding of the time relationship between these two phenomena.

Methods

A total of 15 healthy young women who had normal menstrual histories and normal pelvic structures served as subjects in this study. Eight of these women are of known fertility, two of them having become pregnant during cycles under observation. Most of these subjects were followed through at least three or four cycles, and four of them were studied for from eight to fifteen cycles. Daily observations, save during menstruation, were made whenever possible. The cervical mucus was obtained from the external os and from the cervical canal by aspiration, using the method previously reported.[5, 7] An effort was made to obtain all the mucus available at any one time, and all specimens were weighed. Basal temperature, taken vaginally, were recorded in the usual manner.

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Results

A total of 80 cycles have been observed, and in all of these an increased mucus production was noted at midcycle. As has been reported,[5, 7] the amount of mucus which can be obtained from the canal at a single aspiration is small, ranging from 15 to 50 milligrams, in the pre- and postovulatory phases of the cycle. As the cycle enters the ovulatory phase, the amount of mucus secreted increases markedly and reaches a peak production approximately in the middle of the ovulatory phase. The amount of mucus which can be aspirated at the time of this maximal secretion varies from 113 to 738 milligrams, with an average of 268 milligrams. The quantity then falls to the postovulatory level of 15 to 50 milligrams in two to three days. The individual specimens of mucus were assigned to the different phases of the cycle on the basis of the general knowledge of the cycle as a whole, the amount aspirated, and the degree of cellularity of the sample.

On the basis of quantity and degree of opalescence of the mucus secretion, it was possible to determine the length of the ovulatory phase within one day in 37 cycles. These observations were made on a group of 12 subjects whose menstrual cycles ranged from 22 to 37 days in length. The period of markedly increased mucus production varied from three to seven days, with an average of five days (Table I). It was noted that in 12 cycles of thirty days or more the duration of the increased mucus secretion was never less than five days. The time in the cycle at which this phase of increased mucus secretion appeared was related more closely to the time of the onset of the subsequent menses than to the time of the preceding menstrual period as shown by the fact that the period of increased mucus secretion occurred later in the cycles of longer length (Table II).

The day on which the cervical secretion attained its maximal production was noted in 53 cycles ranging in length from twenty-two to thirty-seven days (Table III). These observations were made on 13 subjects. When the days of the cycle were numbered in the usual manner, i.e., by counting the first day of the preceding menstrual flow as day one, the time of maximal mucus secretion varied from day 9 to day 24. In only some 50 per cent of these cases did the day of maximal secretion occur between days twelve and sixteen after the last menses. This low percentage can be explained by the fact that there is considerable variation in the lengths of the cycles observed. However, when the days of these same cycles were numbered in reverse, i.e., as days before the onset of the subsequent menses, it was found that the maximal secretion occurred over a much shorter range, namely eighteen to eleven days, regardless of the length of the cycle. In 83 per cent of the cycles the variation was only from sixteen to twelve days before the onset of the next menstrual period. This is further evidence that the length of the phase between ovulation and the succeeding menses is more or less fixed at 14 days ± 2,[16] while the length of the preovulatory phase varies with the length of the cycle.

Although the day of maximal secretion varied from 18 to 11 days before the subsequent menses for the entire group, when the cycles of a particular individual were considered separately the range was much less (Table IV). This may be explained by postulating that some individuals consistently appear to have a longer postovulatory phase than others.

Basal temperatures were recorded in a total of 65 cycles on 14 subjects, and all of these showed curves of the diphasic type characteristic of normal women in the reproductive age. In 43 of these cycles the time of the temperature shift from a lower to a higher level was sharply defined. In 14 cycles these transitions were not distinct, although the over-all appearance of the curves were of the diphasic type. These indistinct curves were not limited to

any particular individual, because in other cycles the same subjects had temperature curves with clearly defined shifts. Since the basal temperature is influenced by numerous external factors,[12-14] it is not surprising that the temperature curves are subject to some variation. Although the curves were definitely diphasic in an additional eight cycles, the records were incomplete in the ovulatory phase, making it impossible to determine the exact time of the shift.

The temperature shift occurred later in the longer cycles, and corresponded in this respect with the information obtained from the mucus production studies. The shift occurred from twelve to sixteen days after the onset of the last menses in only 53 per cent of the cycles, the lengths of which varied from twenty-two to thirty-seven days. However, when the days of the cycles were numbered in reverse, as already explained, the temperature shift occurred from sixteen to twelve days (14 days ± 2) before the subsequent menstrual period in 88 per cent of the cycles.

Sufficient information was available to correlate the time of the temperature shift with the period of increased mucus production in a total of 57 cycles in 14 subjects. In 38 of these cycles the temperature shift was clearly defined, and in only two instances did the shift occur at a time when the mucus was not increased in amount. In one of these cases the shift occurred two to three days before the period of increased mucus secretion began, and in the second instance the temperature shift occurred two to three days after the period of increased mucus production had ended.

In 27 of the 57 cycles it was possible to correlate the temperature shift with the day of maximal secretion. In 14 of these cycles the maximal secretion occurred at the time of the temperature shift; in five cycles the maximal secretion occurred one to two days before the shift; and in eight cycles the maximal secretion occurred one to two days later. In the latter two groups, even though the mucus secretion was not at the peak of production, it was markedly increased at the time of the shift.

The exact time of the temperature shift was obscured in 19 cycles by day to day fluctuations even though the entire curves were diphasic in character. However, the increased quantity and the accellular appearance of the cervical mucus that was observed during the period in question suggested that the temperature shift must have occurred at this time.

Discussion

The time when the human female is susceptible to fertilization is probably limited to a very few days in the menstrual cycle; well defined periods of sterility and fertility support this conclusion. While individual variations are admitted, the bulk of evidence, both direct and indirect, places the ovulatory phase when fertilization may occur at about 14 days prior to the next menstrual period.

Basal temperature variations were correlated with phases of the menstrual cycle as early as 1904 by Van de Velde.[17] This shift in temperature from a lower to a higher level, occurring as it does about fourteen days prior to the succeeding menstrual period, has come to be regarded as intimately associated with the ovulatory process.[12-14] Furthermore, it has become a not uncommon clinical practice to instruct women who are planning pregnancies to be especially mindful of the time of the month when the rise in temperature occurs. In this phase of the cycle the entire generative tract undergoes changes adapting it to the fertilization and gestation processes. Among these

TABLE I. DURATION OF OVULATORY PHASE AS DETERMINED BY INCREASED MUCUS SECRETION

NUMBER OF DAYS DURATION	NUMBER OF CYCLES OBSERVED
3	4
4	7
5	11
6	9
7	6

TABLE II. TIME IN CYCLE AT WHICH PERIOD OF INCREASED MUCUS SECRETION OCCURS

NUMBER OF CYCLES OBSERVED	LENGTH OF CYCLES OBSERVED (DAYS)	RANGE OF PERIOD OF INCREASED MUCUS (DAYS)*
1	22	9-14
1	24	9-12
6	25	8-17
2	26	10-14
6	27	10-21
3	28	11-21
6	29	11-19
3	30	13-21
2	31	15-21
2	33	17-23
2	34	15-21
1	35	20-24
2	36	17-25

*The first day of flow in the preceding menstrual period is counted as day one of the cycle.

TABLE III. TIME IN CYCLE AT WHICH MAXIMAL SECRETION OCCURS

NUMBER OF CYCLES OBSERVED	LENGTH OF CYCLES OBSERVED (DAYS)	RANGE OF DAYS ON WHICH MAXIMAL SECRETION OCCURS	
		DAYS SINCE PRECEDING MENSES	DAYS BEFORE SUBSEQUENT MENSES
1	22	11-12	11-12
1	23	12	12
3	24	11-13	12-14
6	25	9-14	12-17
6	26	10-15	12-17
9	27	10-15	13-18
4	28	13-18	11-16
8	29	13-18	12-17
5	30	15-19	12-16
3	31	17-18	14-15
1	33	20-21	13-14
2	34	18-19	16-17
1	35	22	14
2	36	21-23	14-16
1	37	23-24	14-15

changes is the elaboration of a copious cervical secretion of low viscosity and low cell content. Since in vitro tests demonstrate that the cervical mucus secreted in the ovulatory phase is most readily penetrable by spermatozoa, one may be permitted to surmise that a like condition exists in vivo.

The present study indicates that a close correlation exists between the phase of increased cervical secretion and the time of the shift in basal temperature. Both phenomena seem to be under hormonal control, but the fact that the maximal secretion of cervical mucus does not necessarily coincide with

TABLE IV. INDIVIDUAL VARIATIONS IN TIME OF OCCURRENCE OF MAXIMAL MUCUS SECRETION

SUBJECT	NUMBER OF CYCLES OBSERVED	LENGTH OF CYCLES OBSERVED (DAYS)	RANGE OF DAYS ON WHICH MAXIMAL SECRETION OCCURS (DAYS BEFORE SUBSEQUENT MENSES)
6	10	29-37	15-13
5	8	22-30	14-11
7	8	27-31	17-12*
1	4	25-27	18-16
9	4	25-29	17-14
13	3	24-27	16-13
11	3	24-27	14-12
8	3	25-30	13-11
2	3	26-27	16-13
3	2	26-27	17-15
12	2	28-30	16-15
16	2	34-36	17-15

*If the two cycles in which maximal mucus secretion occurred on day seventeen and day twelve, respectively are omitted, maximal secretion occurred on day thirteen or fourteen in the remaining six cycles.

the time of the basal temperature shift is additional evidence that the exact sesquence of events associated with human ovulation are not yet clearly understood. At the present time the only definite conclusion that can be drawn is that in normal women, only rarely does the temperature shift occur when the cervical mucus is not increased.

In planning pregnancy in women of low fertility and in employing artificial insemination it is highly desirable to know when and under what conditions successful insemination is most likely to occur. A study of the cervical mucus cycle together with the basal temperature cycle should furnish valuable information relative to the period of maximal fertility.

Summary

The length of the ovulatory phase in the normal menstrual cycle was determined on the basis of the increased quantity and decreased cellularity of the cervical mucus secreted at this time. This phase of increased secretion was found to vary from three to seven days in length and occurred later in cycles of longer length. The shift in basal temperature was also observed and it was found to occur, with rare exceptions, only during this phase of increased mucus secretion. The day of maximal mucus production usually occurred from sixteen to twelve days before the onset of the subsequent menstrual period regardless of the length of the cycle. When the day of maximal mucus secretion was correlated with the time of the basal temperature shift, it was found that the two phenomena occurred simultaneously in only 52 per cent of the cycles studied. In 18 per cent of the cycles the maximal secretion occurred one to two days prior to the shift, and in 30 per cent of the cycles it occurred one to two days later. A study of the cervical mucus cycle together with the basal temperature cycle has been suggested as a possible aid in planning pregnancies.

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POSTPARTUM HEADACHE AFTER LOW SPINAL ANESTHESIA IN VAGINAL DELIVERY AND ITS TREATMENT

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THE increasing use of spinal anesthesia in obstetrics prompted us to issue a preliminary report in the hope that those cases of headache commonly attributed to the anesthetic may be alleviated by the suggestions to be offered.

Headache following the use of low spinal or saddle block anesthesia for vaginal delivery is an annoying though transitory complication in some cases. The incidence of postlaparotomy spinal headache in cesarean section and various gynecologic operations was found by us to be much lower than in vaginal delivery. In the latter, a headache incidence of 15 per cent was noted in a series of 300 cases. As we were unwilling to forego the many advantages of spinal anesthesia in obstetrics, as set forth in an earlier publication,[1] the mechanism and treatment of the postpartum spinal headache became a practical problem, particularly since it was the only postpartum complaint attributable to the anesthetic. The higher headache incidence in vaginal, as compared with abdominal deliveries, indicated that there were certain factors concerned in its production which do not usually operate in cases subjected to cesarean section or other abdominal operations under spinal anesthesia.

An unusual case of severe and persistent postpartum headache following the subarachnoid administration of 50 mg. of procaine hydrochloride for vaginal delivery first focussed our interest on the necessity for study of this problem.

M. G., primipara, 21 years old, was delivered easily on Aug. 17, 1945, by low forceps of a living female. At 8 cm. dilatation, 50 mg. of procaine were injected slowly into the fourth lumbar interspace. Anesthesia was effective; prompt, spontaneous effacement and full dilatation of the cervix quickly followed; and delivery was uneventful. On the third postpartum day, a mild frontal and occipital headache set in, and grew progressively more severe. Full therapeutic doses of codeine, aspirin, caffeine, benzedrine, ephedrine, gynergen, and ammonium chloride, given at various times, were ineffective throughout her hospital stay of ten days. The puerperium otherwise was normal. On the ninth postpartum day, when she was discharged from the hospital, her headache was unrelieved. On the twelfth postpartum day, pounding in the ears and persistence of headache necessitated continuous confinement to bed at home. Lying flat afforded no relief, and sitting in bed intensified the headache and caused throbbing of an unbearable degree. Examination by one of us (W. A.) on this day disclosed no pelvic or other physical abnormality. Blood pressure in bed was 110/70, and pulse rate 80. On standing upright out of bed she experienced an accession of headache and throbbing in the ears, the pulse rate rose to 130 per minute, and the blood pressure fell to 60/0. This evidence of orthostatic hypotension and tachycardia suggested the application of firm, manual, abdominal compression. Amazing and instantaneous relief of symptoms followed.

Release of abdominal compression was succeeded by prompt recurrence of headache and throbbing. A very tight abdominal binder was forthwith applied to maintain constant compression, and the patient was enabled at once to resume her usual duties unhampered by return of symptoms. This dramatic therapeutic result in the case of an unusually severe postlumbar puncture headache encouraged further investigation of its *modus operandi,* and the following routine was instituted.

Procedure

Three hundred patients delivered vaginally under spinal anesthesia were questioned daily during the postpartum period for the occurrence of headache. As soon as any complaint was registered, the following observations were made:

1. Blood pressure reading and pulse rate lying in bed.
2. Blood pressure readings and pulse rates, one minute and three minutes respectively, after standing out of bed.
3. Effect of firm, abdominal compression on headache, blood pressure, and pulse rate in and out of bed.

As a control, similar observations were made on a group of puerperae in whom no headache had developed by the fifth postpartum day.

Results

Of the 300 patients examined, headache occurred in 45. It was noted that postspinal anesthetic headache in this group most often appeared on the third or fourth postpartum day. Twenty-three of the patients developing headache after spinal anesthesia (slightly over 50 per cent) exhibited orthostatic hypotension of varying degree which was in almost every instance associated with orthostatic tachycardia. No direct relationship was demonstrable between the degree of orthostatic hypotension and/or tachycardia and the intensity of headache. Individual emotional reaction and varying threshold for pain, in addition to certain unknown factors, are probably accountable for this finding. Abdominal compression, at first tentatively by hand to test immediate response, and then, by means of a tight binder resulted in a complete, or almost complete, relief of postlumbar puncture headache in most cases (90 per cent). A many-tailed, abdominal binder, extending from the symphysis pubis to the xyphoid process, reinforced by folded towels inserted between binder and abdominal wall, as required to maintain maximum continuous compression, proved satisfactory. Frequently the patient's own laced, abdominal support, firmly applied, proved equally efficacious.

Determinations of blood pressures and pulse rates did not bear out our early expectation that the headache was invariably associated with orthostatic hypotension and/or tachycardia. While all patients who exhibited orthostatic hypotension and/or tachycardia did develop headache, a considerable number (almost 50 per cent) complained of headache on the third or fourth postpartum day without evidence of a definite fall in blood pressure or marked rise in pulse rate. The essential point of practical application is that firm abdominal compression was efficacious in relieving the headache in either category.

It should be mentioned that a small incidence of postpartum headache and orthostatic hypotension and tachycardia are found irrespective of the use of spinal anesthesia. Chronic sinusitis, dental disorders, constipation, neuralgia, migraine, breast disorders, psychic, and other factors require differentiation in our experience. If spinal anesthesia be administered to patients in this group, the headache may be erroneously attributed to the anesthetic. If headache develops, firm abdominal compression should be applied in any case; and the headache, if it be of spinal anesthesia origin, will almost always be effectively

relieved, while if it be of other origin, it will remain unaffected. If orthostatic hypotension and/or tachycardia are found, the headache is most likely of spinal anesthesia origin. Headaches of other origin were excluded from this study. There is a strong element of suggestion in the development of any postpartum headache, and we have learned from experience that it is wiser not to question for its onset too overtly, but rather by indirection, or to wait until the patient volunteers the complaint. A discreet nurse helps considerably, while injudicious questioning by attendants causes a higher incidence of this complaint.

Discussion

The two factors which we consider responsible in most cases of spinal headache in obstetrics are: first, and more important, the sudden release of intra-abdominal pressure following delivery of the child, superimposed on the action of the anesthetic; and second, spinal fluid leakage. The latter factor can be minimized by the use of a fine gauge needle (No. 22) which permits the fluid to escape slowly in drops.[2] Rapid release of spinal fluid in a stream, such as occurs under increased pressure or with a wide-bore needle (No. 18), is more likely to be followed by headache.

Spinal anesthesia headache is usually attributed to traction by the brain on various pain sensitive structures which anchor it to the cranium. Such traction follows a disturbance in intracranial hydrodynamics initiated by leakage of spinal fluid at the puncture site.[3] Some observers have recently questioned the leakage theory.[4] Nevertheless, our own observations indicate that leakage does play a part in the initiation of the headache. That this is so is evidenced by the fact that the headache usually begins on the third or fourth postpartum day, by which time sufficient fluid has leaked through the defect in the dura to allow the brain to settle down and rest on the cranial bed. Furthermore, when a simple diagnostic tap is performed without reintroduction of spinal fluid, headache usually appears within twelve hours. Were leakage not a factor, this differential in time of onset of the headache would be difficult to explain

The more important factor in the initiation of the headache after spinal anesthesia we believe to be the pooling of blood in the splanchnic vessels induced by the sudden release of intra-abdominal pressure occurring post partum, which is further augmented by the vasomotor paralysis due to the action of the spinal anesthetic on the sympathetic nerves. Though this was not evidenced clinically in all cases by the presence of orthostatic hypotension and/or tachycardia, the relief afforded by abdominal compression in both groups indicated that their ability to make the necessary compensatory vascular adjustments was faulty. The majority of patients (85 per cent) do not develop postspinal anesthesia headache because of a compensatory vascular competence, or minimum spinal fluid leakage, or both.

In several instances it has been possible to predict the onset of spinal headache by observing susceptibility to orthostatic hypotension and tachycardia. The headache is more often observed in the puerpera with a flabby, thin abdominal wall, often with preceding overdistention during pregnancy. In a typical case of spinal postpartum headache firm manual compression of the

abdomen by the examiner gives most dramatic and instantaneous relief. This tentative test is important, for it indicates that maintained firm abdominal compression will successfully alleviate the headache by disengorging the splanchnic pool, correcting the cerebral circulatory imbalance, cushioning the brain, and thereby relieving irritation of the pain-sensitive structures anchoring it to the cranium. It is our belief that the increased return of blood following abdominal compression raises the pressure in the right auricle which, in turn, is transmitted via the jugular veins to the intracranial veins, thereby lifting the brain from its compressed position on the cranial floor. Traction on the pain-sensitive structures is removed and the headache is relieved.

Ephedrine, benzedrine, gynergen, aspirin, codeine, and other drugs which were tried early in this study, proved of little value and were soon discarded. No relief has been observed from massage of the head or neck, a measure which others have found efficacious.[5] That splanchnic dilatation induced by procaine is not the sole factor causing the headache is apparent in those instances of headache which follow simple diagnostic trap. Contrary to a recent report[6] we have observed headaches after nupercaine, and these were also relieved by abdominal compression.

Our explanation of the markedly lesser incidence of headache in cesarean section and other laparotomies is the compression of the abdomen maintained by the surgical dressing, and the more firmly it is applied, the more effective will it be in preventing headache. It is noteworthy that following hemorrhoidectomy after which no postoperative abdominal pressure by the dressing is applied there is for the same reason a higher incidence of spinal anesthesia headache than after laparotomy.

The headache may be frontal, temporal, or occipital. Throbbing in the head is produced or accentuated on sitting or standing. Sometimes the main complaint is stuffiness in the ears. In other cases, there is little headache but stiffness in the nape of the neck or shoulder muscles predominates due to traction on the upper cervical nerves. The therapy suggested has been effective in all types of complaint.

Our prophylactic orders for headache post partum consist of (1) immediate postpartum application of a medium sized sandbag to the abdomen, (2) firm abdominal binder twenty-four hours post partum to be reinforced by folded towels, particularly in the scaphoid abdomen. Frequent resetting of the binder to maintain firm pressure as the abdomen involutes or the patient shifts position is essential for effective results. It is advisable to continue the use of the binder until the patient is discharged from the hospital on the seventh to the tenth day.

Summary

1. The increasing use of spinal anesthesia in obstetrics renders timely the suggestions to be offered for alleviation of post lumbar puncture headache.

2. A headache incidence of 15 per cent was noted in a series of 300 obstetric cases after low spinal or saddle block procaine anesthesia.

3. A higher headache incidence in vaginal, as compared with abdominal, deliveries and various gynecologic operations indicated that there were factors conducive to its production in vaginal deliveries.

4. A case of unusually severe and persistent postlumbar puncture headache exhibiting orthostatic hypotension and tachycardia was effectively relieved by firm abdominal compression. This case initiated investigation of the cause and treatment of this type of headache.

5. The routine investigation adopted in all cases of headache is outlined.

6. Over 50 per cent of patients developing headache exhibited orthostatic hypotension and/or tachycardia, but the intensity of headache bore no direct relationship to the degree of hypotension and/or tachycardia.

7. A many-tailed abdominal binder or other form of firm abdominal support proved equally efficacious in the relief of the headache.

8. Almost 50 per cent of the patients who complained of headache exhibited no evidence of orthostatic hypotension and/or tachycardia. Firm abdominal compression relieved the headache in this group also if it was of spinal anesthesia origin.

9. Causes of headache other than spinal anesthesia are enumerated. The therapeutic effect of firm abdominal compression may be utilized in differential diagnosis.

10. The two factors responsible for the headache are: first, and more important, the sudden release of intra-abdominal pressure following delivery, superimposed on the action of the anesthetic; and second, spinal fluid leakage. The mechanism of both factors is discussed.

11. The inefficacy of various drugs and local massage is noted.

12. The prophylaxis of postpartum spinal anesthesia headache is given.

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4506 Twelfth Avenue

VAGINAL HYSTERECTOMY SUBSEQUENT TO EXTRAPERITONEAL CESAREAN SECTIONS

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SOME unusual aspects provide the interest in which the following case is reported. Anatomic data is given on pelvic fascia as found at vaginal hysterectomy some four years after a second extraperitoneal cesarean section. The vaginal approach provided new observations to the writer and more clearly defined certain statements hitherto regarded as probably true.

The past history was of especial interest in the light of subsequent findings. This patient was first seen on June 21, 1940. She had been in labor for twenty-nine hours, membranes ruptured thirty-six hours, and the fetal heart sounds had not been heard for four hours. The fetal head was dipping but unengaged, the cervix thick, dilated 5 cm., and a foul vaginal discharge was evident. The patient was exhausted, with rapid pulse, temperature 101.4° F., and in very severe labor. She was given sedation, fluids intravenously, chemotherapy, a transfusion readied, and after a period of six hours a supravesical extraperitoneal section of the Waters' type performed. A large stillborn fetus was delivered. Despite a transient infection at the drain site, she recovered rapidly.

On March 30, 1941, she had a spontaneous two months' abortion. She was referred again for care in October, 1941. Examination showed a normal two months' pregnancy. Her pelvis was considered a small android type, subsequently confirmed by x-ray. Elective section was done on May 21, 1942, one week before term. A Waters' type extraperitoneal cesarean section was chosen to determine its feasibility as a repeat operation. Moderate difficulty was encountered from the previous operative adhesions in the retrovesical area, but operation was completed without complication in forty minutes. The drain was removed in forty-eight hours, she was up on the eighth day, and discharged from the hospital on the eleventh postoperative day.

The first notation of symptoms which eventuated in vaginal hysterectomy was on Aug. 17, 1945. This 40-year-old patient had been having terrific labor-like menstrual cramps for six months. Menstruation lasted five days and was regular, but the flow was heavy and clotted. Examination showed a tight nulliparous-type introitus and vagina, a small, closed, clean cervix, and a moderately enlarged uterus with a golf-ball sized intramural fibroid. Hysterectomy was advised on the basis of the findings and symptoms.

She was next seen eleven months later, stating that all pain had stopped several months after the last visit but the menstrual flow had become extremely heavy, prolonged from ten to eighteen days, and associated with the passage of large clots.

Examination now disclosed a vaginal vault filled with a large fibroid, 10 cm. in diameter, prolapsed through a dilated cervix, with the uterus comparable in size to a two months' pregnancy and containing other small fibroids. She was markedly anemic, with a hemoglobin of 50 per cent and 2.3 million red blood cells. Prompt operation was clearly needed.

Alternative measures were vaginal myomectomy followed at a later date by an abdominal hysterectomy, or vaginal myomectomy-hysterectomy with suitable precautions.

Operative Findings.—Operation was done Aug. 5, 1946, under spinal anesthesia. A posterior vaginal incision and perineotomy was needed to gain enough operating room in the nulliparous tight vagina. The fibroid filling the vaginal vault was seized, morcellated, and then resected at its uterine base with long scissors. Uterine cavity and vagina were antisepticized and the cervix closed. Vaginal hysterectomy was completed with moderate difficulty, for the left uterine artery escaped briefly when its ligature was inadvertantly cut by the vault-suturing needle. The posterior vaginal and perineal incisions were closed.

While mobilizing the bladder preceeding the hysterectomy, no alteration was noted in the usual fixation of bladder to cervix by endopelvic fascia, nor in the clear development of the pubocervical ligaments after upward displacement of the bladder. There was no increase in bladder base vascularization nor difficulty in lateral separation of the bladder from the broad ligaments. When the bladder was retracted and displaced higher and away from the lower uterine segment, a few rather tough adhesions near the left broad ligament base were encountered. The vesicouterine fold was somewhat higher than ordinary, but not of notable concern in the operative procedure.

Comment.—From this case, it is evident that in a supravesical extraperitoneal cesarean section, the fascial dissection and incision neither involved nor impaired the bladder-fascial support, but were confined to the enveloping layers or fascia propria of the bladder itself. Likewise, such fascial incisions as are made over the lower uterine segment are well removed from any endopelvic fascial supports. Therefore, in subsequent operative procedures requiring mobilization or utilizaiton of the supporting ligaments, as in vaginal hysterectomy, there would be no involvement or alteration of these structures, nor disturbing interference with the operation itself.

Follow-up Note.—The patient was re-examined on Jan. 27, 1947. A very firm nulliparous introitus was noted, with a deep vaginal vault and strong posterior wall repair. Examined standing and straining, there was no weakness of the anterior and posterior vaginal walls nor of the vaginal vault.

A case is reported of vaginal hysterectomy, subsequent to two supravesical extraperitoneal cesarean sections. Such cesareans require incisions and dissections in the enveloping visceral endopelvic fascial tissues, but not of the supporting portions of the endopelvic fascia. Vaginal hysterectomy done for subsequent tumorous degeneration determined that the supporting fascia and ligaments of the endopelvic fascia were unaltered and uninjured by the previous extraperitoneal operations. No significant change in relationship of bladder and uterus occurred. Previous extraperitoneal cesarean section should not be considered a contraindication for vaginal hysterectomy.

39 Gifford Avenue

AN EVALUATION OF THE TWO-HOUR RAT TEST FOR PREGNANCY*

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THE first accurate pregnancy test was not available until Aschheim and Zondek made their basic observations on gonad stimulating substances in pregnancy urine[1] and in 1928 proposed the pregnancy test[2] which bears their name. Certain disadvantages of this highly accurate biologic hormone pregnancy test caused the originators[3, 4] and others[5] to describe tests that were shorter, more convenient, or more applicable for the average laboratory. Of these tests, the Friedman rabbit and Hogben frog tests are the most widely used today. The inconveniences of these two tests and the objections to the test animals led more recently to the proposal of the rapid rat ovary hyperemia pregnancy test. The rat as a pregnancy test animal offered numerous accepted advantages in care and cost as well as that of increased sensitivity to gonadotropins.[6]

The positive end point of the test, hyperemia of the ovary, is the first gonadotrophic reaction to appear after the parenteral administration of the urine of pregnant women, and is noted suitably in the rat ovary only.[4, 7] This reaction appears in two hours and persists for thirty-six hours. Furthermore, hyperemia of the rat ovary has been reported[7] to be present after the administration of luteinizing and luteotrophic gonadotropins but not after the use of the follicle stimulating hormone.

The advocates of the rapid rat pregnancy test have shortened the time from thirty-six to two hours, and have maintained with few exceptions an accuracy close to 100 per cent. In 1931, Eberson and Silverberg[8] reported a rapid rat-ovary pregnancy test at thirty-six and twenty-four hours with the subcutaneous and intraperitoneal injections of a urine extract. Reiprich,[9] the Walkers,[10] and Kelso[11] used unconcentrated urine and observed favorable results at twenty-four and thirty hours. The results of Frank and Berman[12] at twenty-four hours were comparable with the Aschheim-Zondek test and better than the rabbit test. They were accurate at eight hours, and later[13] were obtainable in four hours. Salmon and his co-workers[14] described a six-hour test which was correct in 108 of 109 cases. Salmon stated in a personal communication[15] that the test was positive in two hours in 95 per cent of the cases. The six-hour test was found by other investigators to be simpler than,[16] comparable to,[17] and as reliable[18] as the Friedman test. Kupperman and his co-workers[19] in 1943 and later[7, 20] reported a 99.5 per cent accuracy with a two-hour rat test in which they favored the intraperitoneal over the previously used subcutaneous route of injection to allow more complete and rapid absorption of the gonadotropins.

However, Farris[21] found the two-hour rat test to be positive in some males and nonpregnant females. Zondek[4] compared the two-, six-, and twenty-four-hour rat tests, and reported the two- and six-hour tests to be inaccurate. Kup-

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perman and Greenblatt[7] were unable to confirm the findings of Farris in males and nonpregnant females, and objected to the subcutaneous avenue of injection by Farris and Zondek in judging the accuracy of the two-hour rat test. Kupperman and Greenblatt,[7] too, noted the test to be only 65 per cent accurate with the subcutaneous injection, but obtained excellent results with the intraperitoneal route. However, Salmon[15] states that the accuracy is 95 per cent at two hours with the subcutaneous injection.

Purpose and Procedure

The purpose of the study was to determine the reliability of the two-hour rat pregnancy test as a routine procedure for the average laboratory. The two-hour rat test was performed on each of 228 specimens of urine sent to the Endocrine Laboratory of the Jefferson Hospital in 200 ward, clinic, and private cases, for a Friedman pregnancy test. A total of 390 rats was used and examined before the Friedman tests were completed. Rat tests with one rat were performed in the first 124 cases, and the Friedman tests awaited. If there was a discrepancy with the Friedman test, or a doubtful reaction, additional rats were used. In the suspected ectopic pregnancy cases two or three rats were used, and this number of animals was routinely employed later in the study. Two rats were used with each specimen in a comparative study of the two-, six-, and twenty-four-hour rat tests. One rat was opened in two hours and the other in six or twenty-four hours. A clinical diagnosis was obtained for corroboration four to nine weeks later in 195 of the 200 cases.

Technique.—The technique followed in the two-hour rat pregnancy test was that advised by Kupperman and Greenblatt.[7] Immature albino female rats 21 to 30 days of age, and 30 to 60 Gm. in weight were used. While the rat was held posteriorly 2 c.c. of an unaltered morning specimen of urine was injected intraperitoneally in divided doses of 1 c.c. each into the right and left lower abdominal quadrants. Two hours later the animal was killed by ether asphyxiation. At autopsy the intestines were displaced, and the ovaries readily exposed. The test was considered negative if the ovaries were pale or pinkish—and positive if one or both of the ovaries were light to dark crimson. The six- and twenty-four-hour tests were modified in that an intraperitoneal, rather than a subcutaneous route of injection, was used.

Results and Discussion

Normal Intrauterine Pregnancy.—In the 87 normal intrauterine pregnancies there were three errors in the Friedman tests, and four errors in the rat tests—giving an accuracy of 96.4 and 95.4 per cent, respectively, (Table I). The errors in the Friedman and rat tests occurred in different cases so that if one was incorrect, the other was correct. Using other specimens four to eight days later. three of the errors, one rat and two Friedman tests, were corrected. In three cases positive tests were noted seven days after the expected date of the first missed menses.

Ectopic Pregnancy and Abortion Cases.—Variances between the Friedman and rat tests were noted in the group of 35 clinically proved cases of disturbed pregnancy—such as abortions, ectopic pregnancy, and intrauterine fetal death (Table I). There were no false positive or negative rat tests, but there were four false negative Friedman tests, of which three occurred in the abortion and one in the ectopic pregnancy groups. Zondek[4] stated that the rat hyperemia test is especially sensitive for the diagnosis of pregnancy, since the test is evoked with one-third of the pregnancy urine gonadotropin that is necessary for luteinization (Aschheim-Zondek test). It would seem, therefore, that the rat test would

TABLE I. —COMPARISON OF THE TWO-HOUR RAT AND FRIEDMAN PREGNANCY TESTS

FINAL CLINICAL DIAGNOSIS	NUMBER	FRIEDMAN		RAT	
		POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Normal pregnancy	87	80	3*	83	4†
Ectopic pregnancy	8	5	1‡	8	0
Threatened abortion	12	7	2‡	12	0
Incomplete abortion	10	1	8§	2	8
Intrauterine fetal death	5	3	2	2	3
Nonpregnant	78	0	75	0	78
Totals	200	96	91	107	93

*Two repeat specimens positive.
†One repeat specimen positive.
‡False negatives.
§One false negative.

be of especial value in those cases of disturbed pregnancy in which the gonadotropin levels were low. However, Zondek[4] further stated that the rat test is adequately accurate for the determination of cases of undisturbed pregnancy, but insufficient for cases of disturbed pregnancy. He reported inaccurate results with the two-hour rat test in four cases each of ectopic pregnancy and abortions.

As a rapid diagnostic test for pregnancy, the two-hour rat test attains its purpose as an aid in the detection of ectopic pregnancy. This fulfills the wish of the clinician who cannot wait for one of the more time-consuming pregnancy tests, but who wishes confirmation of his diagnosis by a pregnancy test. There were 28 cases in which ectopic pregnancy was considered as the primary diagnosis. This was the final diagnosis in eight cases, as confirmed by operation. The rat test was correct in these proved cases, while the Friedman test was incorrect in one case (Table II). In this group of 28 cases, the Friedman test alone would have been misleading and time consuming. In the 24 cases in which Friedman tests were done, there were two false negative tests in the ten cases of disturbed pregnancy, and two doubtful tests in the twelve nonpregnant cases. Kupperman and Greenblatt[7] reported an 88.3 per cent accuracy with the two-hour rat test in eighteen cases of ectopic pregnancy.

TABLE II. COMPARISON OF FRIEDMAN AND TWO-HOUR RAT PREGNANCY TESTS IN POSSIBLE ECTOPIC PREGNANCY CASES

FINAL DIAGNOSIS	NUMBER OF CASES	FRIEDMAN		RAT	
		POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Ectopic pregnancy	8	5	1*	8	0
Pelvic inflammatory disease	8	0	8	0	8
Abortions	4	1	3†	2	2
Fibroids	2‡	0	1	0	2
Menstrual disturbances (Endocrine)	4‡	0	3	0	3
Intrauterine pregnancy	2	2	0	2	0

*False Negative.
†One False Negative.
‡One Doubtful Friedman—not repeated.

Nonpregnant Cases.—The rat and Friedman tests were negative in the 78 nonpregnant cases. The nonpregnant cases included diagnoses of menopause, pseudocyesis, endocrine menstrual disorders, psychoses, fibroids uteri, pelvic inflammatory disease, ovarian tumors, and carcinoma of the genital tract. This group included the types of cases in which Zondek[13] noted and in which Greenhill[22] stated that false positive pregnancy tests may occur.

Farris[21] reported false positive rat pregnancy tests in some males and nonpregnant females. The present series included the menopausal and psychoses cases in which Farris noted false positive rat tests. Others were unable to confirm the findings of Farris in males[7] and in females at midcycle.[7, 12]

Comparison With Six- and Twenty-four-hour Rat Tests.—In a small series of 47 cases the two-hour rat test compared favorably with 39 six-hour, and 8 twenty-four-hour rat tests. The two- and six-hour rat tests each had three false negative tests, while there were two in the twenty-four-hour tests. If the two-hour test was incorrect, the six- or twenty-four-hour test was correct and, if either of the latter was incorrect, the two-hour test was correct.

Toxic Reactions.—The rat is more tolerant to toxic specimens of urine than is the rabbit. Five rabbits and two rats died as the result of toxic specimens for percentages respectively of 2.2 and 0.8. Ramsey[18] noted toxic reactions in 3 per cent of the rabbits, and 0.5 per cent of the rats. In considering possible repetition of tests, it was noted that there were doubtful reactions in 2.3 per cent of the rabbits and 5 per cent of the rats.

False Negative and Doubtful Reactions.—Two rats were used for each test by others. These studies suggest the need for three rats per test due to the number of false negative and doubtful reactions. The use of three rats increases the cost to approximately that of the rabbit test, and decreases the simplicity of the test. One rat was used initially in 124 cases, but 24 tests were repeated because of thirteen doubtful reactions three slow responses in the positive group and eight variations with the Friedman test. In the group of eight variations, there were correctly two positive and six negative rat tests, in contrast to two negative and six positive Friedman tests. In each repeat test, urine from the original specimen was injected into two rats. On repetition the three positive slow responses remained positive, while in the group of thirteen doubtful reactions there were two positive and eleven negative tests. In the group of eight tests which had varied with the Friedman tests, the two positive rat tests remained correctly positive. Three of the six false negative rat tests persisted as false negative. The other three false negative tests were positive on repetition. In two of these three positive cases, four of the six rats failed to respond.

In a group of 55 cases, two rats were used per test. There were no false tests, but nine rats failed to react in 33 positive cases. Three rats were used in each of 21 cases of possible ectopic pregnancy. The rat test was correct in all. In the fifteen positive cases there were fourteen false negative and four doubtful reactions. As many as six of these cases may have been added to the error group if only two rats had been used. Therefore, with the advised use of two rats, the error group with three rats may have been increased by 200 per cent to give a very unsatisfactory percentage of accuracy.

As noted by others[7, 12, 14, 15, 19, 20] when the rat test reaction was positive, it was conclusive. However, negative reactions were inconclusive. The percentage of false negative rats was high. While in other series[7, 12, 15] the number ranged from 0.2 to 3.8 per cent, it was 10 per cent in this group of 390 rats. The 40 false negative and 20 doubtful reactions were 15.4 per cent of all rats used. The 40 false negative reactions occurred in 23 per cent of the positive cases and were equally distributed between 13 cases of normal intrauterine pregnancy and 14 cases of complications of pregnancy. Of all negative reactions, 19 per cent were false. As a result, there was a feeling of uncertainty in reporting negative reactions and tests.

Interpretation of the Test.—Another point of difficulty involves the reading of the test. The test ovaries vary in color so that Kline[16] has listed four negative, one doubtful, and four positive shades while Farris[21] noted six variations. The typical crimson positive and pale negative are distinct. However, the shades between these are difficult to interpret and may be responsible for a false reading.

Conclusions

On the basis of this series, the two-hour rat pregnancy test is noteworthy because of:

1. The rapidity with which the result may be obtained.
2. The increased sensitivity of the test as noted by the accuracy in cases of disturbed pregnancy.
3. The rarity of false positive tests.
4. The increased tolerance of the rat to the toxic specimens of urine.
5. The conveniences of the test and the test animals.

However, further investigation is necessary to:

1. Further increase the accuracy of the test since it ranged below the Friedman test in normal intrauterine pregnancies.
2. Obviate the large number of false negative and doubtful reactions which caused a feeling of uncertainty in reporting negative tests.
3. Increase the color intensity of positive reactions.
4. Lessen the need for three rats per test.

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A METHOD OF DELIVERY FOR HYDROCEPHALUS ASSOCIATED WITH BREECH PRESENTATION

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THE method to be described was suggested by a description in Stander's *Obstetrics*,[1] and differs from this only in minute detail. It is therefore presented not because of originality, but rather because its extreme simplicity and safety warrant for the procedure a more general acceptance than it has received. A recent case is the impetus for this report.

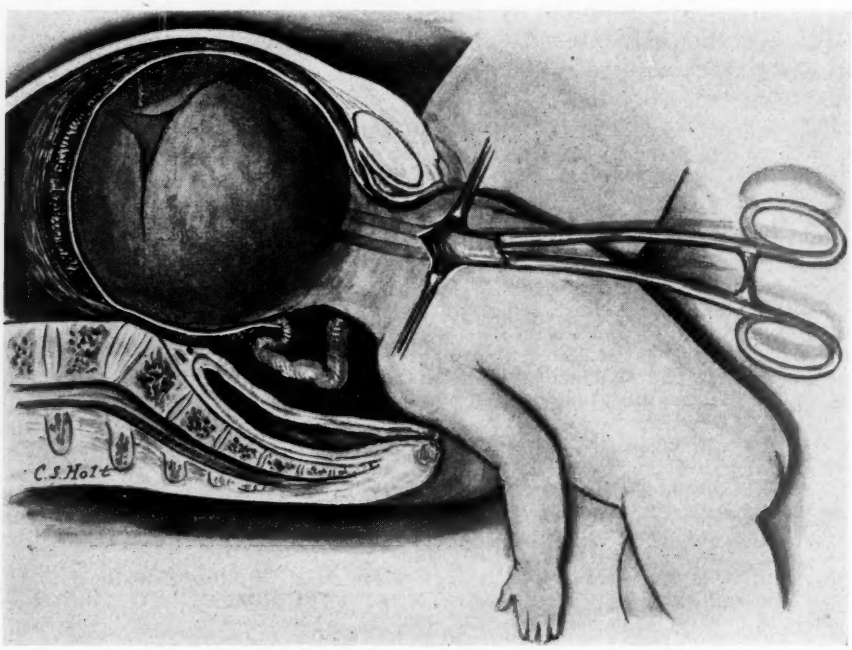

Fig. 1.

Method of Delivery.—If the case is one of frank breech, the breech is allowed to advance and is delivered according to accepted procedure, with one exception: since the labor is to end by stillbirth, it is permissible to spare the patient the necessity of delivering the breech by voluntary effort. This may be accomplished, when the breech approaches the perineum, by making traction in the groin with a blunt hook. Delivery of the breech and of the shoulders is then completed as under ordinary circumstances. No attempt is made to cause the head to engage more deeply. A Jackson retractor is placed anteriorly, and the highest spinous processes which one can visualize are palpated. An incision is made in the midline over two of these processes, which ordinarily are those of the lower cervical or upper thoracic spine. The skin edges are retracted by Allis forceps, and a laminectomy performed over these two segments. (This is readily accomplished in the fetus by incision through

the laminae with a scalpel, and removal of the fragment with a small rongeur.) The tip of a uterine dressing forceps—which is considered as preferable to the catheter as mentioned in the original description—is introduced into the opening in the spinal canal and forced gently but firmly upward into the cranial cavity. It is rotated to enlarge the canal, and the blades are separated slightly. By making pressure upon the head from above, cerebrospinal fluid is caused to issue from the laminectomy wound. This is continued until either the flow of fluid stops, or the collapsed head advances sufficiently that it can be delivered. The dressing forceps is now withdrawn, and the head delivered by the Mauriceau maneuver.

The procedure is simplicity itself. Since it is done under direct vision without possibility of injury to the maternal soft parts by bone spicules, it is considered as preferable to the more popular approach with the customary perforator behind the ear or through the lamboidal suture.

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FULL-TERM PREGNANCY FOLLOWING OPERATION FOR CONGENITAL ABSENCE OF VAGINA*

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ANOMALIES of the genital tract are always of interest. Some of these anomalies may be associated with primary amenorrhea and sterility, particularly when there is nonunion of the Müllerian system with the ectodermal vaginal inpouching. The imperforate hymen is the simplest of the defects encountered in this group. More or less complete absence of the vagina, even in the presence of a functioning uterus, as evidenced by hematometra, is not unusual. A connection can always be established surgically between uterus and vulva, and usually coitus can be made possible. However, the subsequent occurrence of pregnancy following such surgical procedures is extremely rare. Only two reports of such an event have been found in the literature. In one[1] a cavity was created between the rectum and the bladder. Skin flaps from the thighs and labia were used for lining this cavity. The patient became pregnant and was delivered at term by cesarean section. In the second report[2] a segment of sigmoid was interposed between the uterus and the vaginal pouch. The patient was delivered spontaneously of three children, the last weighing 4,500 grams.[3]

The present report concerns a patient who was first seen in 1937 at the age of 16 years, complaining of primary amenorrhea. Her identical twin sister had been menstruating normally for approximately two years. Examination revealed a complete atresia of the upper two-thirds of the vagina. The lower pole of a palpable abdominal mass was separated from the apex of a small vaginal pouch by a distance of 5 to 6 centimeters. The mass, approximately the size of a sixteen-week pregnancy, was interpreted as being a dilated uterus containing retained menstrual blood. Under anesthesia, the tiny vaginal vault was split transversely and by blunt and sharp dissection a cavity was created between the bladder and rectum. The lower pole of the mass was incised and approximately twelve ounces of retained black menstrual blood escaped. The uterus was then anchored to the vaginal pouch with mattress sutures. Recovery was uneventful and normal menses followed. Postoperative examination revealed a short, narrow vagina with the lower pole of the uterus flush with the vault. No vaginal cervix existed.

This case was previously reported by one of us (Baer) before this Society on Dec. 17, 1937.

The patient married in 1941. Conception followed the elimination of contraception in 1946. Pregnancy progressed uneventfully and, since there was neither detectable cervix nor a detectable cervical os in the vaginal vault at term, an elective cesarean section was performed. She was delivered of a normal 7 lb., 15 oz., male by laparotrachelotomy. At operation, a well-formed lower uterine segment was found, and the pelvic genitals were normal in all respects except for very superficial tortuous ovarian arteries coursing along the infundibulopelvic and upper broad ligaments. After the contents of the uterus had been evacuated and the bleeding controlled, the cervical canal was located and readily dilated to number 10 Hegar. Postoperative convalescence was uneventful.

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The simple primary operative procedure described here served several very useful purposes: (1) it provided an outlet for menstrual blood; (2) it provided a canal for coitus, and (3) it made impregnation possible.

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BILATERAL SIMULTANEOUS TUBAL PREGNANCY

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BILATERAL tubal pregnancy is infrequent, for a total number of 84 authentic cases have been reported since 1890, up until and including 1945. A survey of records at the hospital with which I have been affiliated for the past twenty-five years has no incidence of any case of bilateral tubal pregnancy during that time.

D. B., aged 35 years, a married white woman, consulted me on Dec. 6, 1946, complaining of vaginal bleeding and pelvic pains. The bleeding began about three weeks prior to consultation, although she ignored it and continued working. About November 29 her pains became more annoying, colicy in type, and of short duration, although she rested comfortably at night. From the time of the onset of bleeding until November 29 most of the time she was without pain, but continued to have vaginal spotting. About five days before I saw her, the pains became more severe, also the bleeding at times was on the increase. Her menses were always regular, occurring every 28 days and lasting 7 days, with occasional premenstrual cramps. She had had one normal delivery in 1934. Her general health was always good. A thyroidectomy was done in 1940. Since then she had been more or less nervous. Examination of this patient revealed that she was acutely ill with a temperature of 99° F., pulse rate of about 90, and respiration 22. Extreme tenderness was elicited on palpation over the entire lower abdomen, more marked in the right lower quarter, and intensified on deeper palpation and percussion. Vaginal examination revealed very little; the cervix was soft, but, due to increased discomfort, it was impossible to do a thorough examination. The patient agreed to be hospitalized for further study. She was admitted to the hospital in the afternoon on the same day. The temperature on admission was 99.2° F., pulse 90, respiration 22, blood pressure 110/70. Urinalysis: acid, sp. gr. 1030, albumin trace, sugar negative. Microscopically: hyaline casts, loaded, granular, many. Complete blood count hemoglobin, 83 per cent; red blood cells 4,400,000; white blood cells, 11,000; C. I., 0.94; differential band, 13 per cent; neutrophiles, 62 per cent; lymphocytes, 25 per cent. During the night the patient rested comfortably. The following morning a repeat blood count was hemoglobin, 66 per cent, red blood cells, 3.85; white blood cells, 15,600; band, 17 per cent; neutrophiles, 71 per cent; lymphocytes, 12 per cent. Preoperative diagnosis of ruptured right tubal pregnancy was made. All preparations for blood transfusion and plasma were instituted. Under spinal anesthesia a midline suprapubic incision beneath umbilicus was made. Considerable amount of free blood with clots was found in the abdominal cavity. The right tube was involved in the outer third, considerably distended, and bleeding from the fimbria with placental tissue showing at the opening. The tube was carefully released from its adherence to the ovary and removed with cornual resection. The left tube was considerably distended at its outer third, but sealed at the fimbria. This was also removed with cornual resection. During the operation the patient received 1000 c.c. of saline with 5 per cent glucose. The time of operation consumed twenty-eight minutes. Upon returning to her room she was given 500 c.c. of plasma.

Pathologic Report.—Specimen consisted of both tubes and a small mass of spongy placental-like tissue. The fimbriated end of one tube revealed the

presence of a protruding saclike structure in which there was a tiny rent. The lumen was found to be dilated. The fimbriated end of the other tube was congested, and there was some spongylike material present which covered the lining.

Microscopic examination of a section of tube revealed a marked thickening of the walls due to fibrosis, fatty infiltration, and edema. The mucosal papillary structures were flattened and markedly distorted. There was a moderate infiltration of the mucosal papillary structures with lymphocytes. Another section of tube showed considerable distortion of all the normal histologic structures and an infiltration of the walls with decidual cells. There were also a few well-defined chorionic villi present. A section of tissue expressed from the tube revealed it to be definitely placental in character. It was made up of large edematous appearing chorionic villi.

Diagnosis: Bilateral tubal pregnancy. The patient's postoperative course was uneventful. She was discharged from the hospital on December 17 and classified as recovered. Subsequent to her leaving the hospital, she was seen at her home, and also at my office on Jan. 6, 1947, and her last office visit was Feb. 3, 1947, at which time she was fully recovered.

SIMULTANEOUS TUBAL ABORTION AND UTERINE PREGNANCY

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THE concomitant existence of uterine and tubal pregnancy is rare. Parry[1] states that out of 500 cases of tubal pregnancy 22 were simultaneous with uterine pregnancy. He called such a condition as combined pregnancy in contradistinction to the term compound pregnancy which is applied to cases of intrauterine pregnancy superimposed on a previously existing ectopic pregnancy that has terminated in lithopedion formation.

On summarizing the cases in the literature as published successively by Novak[2] in 1926, Gemmel and Murray[3] in 1933, Mathieu[4] in 1937, Ludwig[5] in 1940, and Howard[6] in 1945, there are 356 and, with the addition of the present case, presented for the first time in the Philippines, the total up to 1946 is 357 cases.

Double ovum twins are of frequent occurrence in uterine pregnancies. This may explain the existence of concomitant tubal and uterine pregnancies; the difference of the two conditions being only in that one ovum is implanted in the tube and the other in the uterus. But since the site of implantation is different, one being tubal, and the other uterine, the time of impregnation must also be different. In other words such a combined pregnancy must be the result of superfecundation or the impregnation of the ova on different occasions. When the uterine pregnancy is older than the extrauterine one, the difference of the two at the most is less than three months. The reason for this is that at the end of three months the uterine cavity becomes obliterated by the close application of the decidua capsularis with the decidua vera rendering impossible the uterine passage of the spermatozoon. The uterine pregnancy can be over three months older than the extrauterine pregnancy only if the extrauterine pregnancy fails to grow and causes no abnormal symptoms while the uterine pregnancy proceeds in its development towards term. The usual fate of a tubal pregnancy, however, is that it ends in either tubal abortion or tubal rupture long before it reaches the third or fourth month.

For the reasons given above, it is hard to explain the great discrepancy of age of the case reported by Clarke[7] and the one reported by Moudry and associates.[8] In Clarke's[7] case, the tubal pregnancy was two months old while the uterine pregnancy was at term. In Moudry's[8] case the tubal pregnancy was five weeks and the uterine pregnancy was eight months. Both cases presuppose that the tubal impregnation took place when the uterine pregnancy had advanced to at least six months long after the complete obliteration of the uterine cavity rendering impossible the ascent of the spermatozoon. The only explanation possible is either that the spermatozoa can live many months in the pelvic cavity or in the tube and impregnate later, or that the tubal pregnancy became arrested in its growth and failed to show signs of rupture until after many months. Either event, if possible, is indeed very unusual.

Case Report

L. A., 30 years old, was admitted to the Philippine General Hospital on Sept. 11, 1945, because of hypogastric and lumbar pains, slight vaginal bleeding, the general weakness.

She had had ten pregnancies, all ending in full-term deliveries. The last child was 2 years and 9 months old at the time.

Her last menstrual period occurred in the latter part of May, 1945. In July she had morning sickness in the form of nausea and vomiting. In the middle part of August she had slight vaginal bleeding for three days. And for the last nineteen days she has been having abdominal and lumbar pains and general weakness.

Her mother died of pulmonary tuberculosis.

Physical examination showed impairment of breathing over the right interscapular and base regions, muscular rigidity and tenderness over the lower abdomen, specially on the right side. The fundus uteri could be palpated two fingerbreadths above the symphysis. Vaginal examination showed the uterus to be enlarged to the size of two months' pregnancy, and at the right fornix could be felt a tender sausagelike mass.

The diagnosis on admission was pregnancy at 2 months complicated by acute salpingitis of the right tube. So she was given sulfonamides, bromides, and vaginal douches. Her abdominal pains improved, but suddenly on the ninth day after such treatment she had acute abdominal pain and much tenderness in the somewhat full right fornix. She was immediately operated upon.

On laparotomy, much fresh and clotted blood was found in the peritoneal cavity. The right tube was very much enlarged and congested and filled with dark clotted blood mixed with chorionic tissue which was being extruded through the infundibulum. The right ovary, left tube, and left ovary were normal. The uterus was enlarged to the size of a two months' pregnancy.

The postoperative diagnosis was tubal abortion, one month; uterine pregnancy, two months.

Except for slight vaginal bleeding on the third day which, however, subsided after two days, and a slight evening rise of temperature, her recovery was smooth, and she was discharged on the eighteenth postoperative day.

In the follow-up, however, she told us that one month after she returned home when she resumed her household activities, she aborted. Her usual menstruation reappeared one month after her abortion. She was seen in January, 1946. Her uterus then was small and completely involuted. Except for the persistence of her cough, she was in fair condition. In January, 1947, she was again examined internally. The uterus was small. Her menstrual periods continued to recur monthly and without pain. She was referred to the antituberculosis clinic for her cough, chest oppression, and afternoon rise of temperature.

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Special Article

AN OUTLINE OF THE CONDUCT OF PHYSIOLOGICAL LABOR*

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WHEN parturition is neither inhibited nor disturbed by mechanical, chemical or psychological factors it may be termed physiological labor.

All interference when there is no inhibitory or disturbing factor superimposes a pathologic state upon a physiologic function.

Mechanical and chemical abnormalities are observed and treated according to the principles of good obstetrics—such conditions are relatively rare. Psychological and therefore psychosomatic aberrations are seldom diagnosed or treated before or during childbirth. They complicate the large majority of labors. They are the direct cause of interference in 90 to 95 per cent of maternity cases, thereby being responsible for much maternal and infant morbidity and some mortality.

Physical injuries sustained during labor are carefully repaired because it is recognized as essential for the future health and marital happiness of the woman. Psychological injury sustained during labor is neither avoided nor repaired, yet it is not generally recognized that, because of this obstetric oversight, the future health and marital happiness of thousands of women are being destroyed every year. By consideration for the psychosomatic aspects of labor, maternal morbidity is decreased mainly because interference is minimized. The decline in infant morbidity is appreciable, and is largely due to the fact that forceps operations, deep narcosis, and prolonged anesthesia are seldom required for delivery of the child. Physiologic mothers, with few exceptions, insist upon breast feeding their babies—a conscious sense of achievement and pride makes childbirth an event to be repeated and not avoided. One or two child "families" are unsatisfying, for these women and the absence of frustration or feeling of "having let her child down" enables a normal development of the instinct and philosophy of motherhood which in turn stabilizes family life upon which the future progressive development of human society depends.

What are the procedures that we employ to enable a woman to have her child in this way? It is necessary that a woman should not be just a passive subject for treatment but a properly prepared and educated collaborator in the birth of her child; therefore, at the time when labor starts she will have been prepared by understanding the signs and symptoms of commencing labor. She will have been told that the boredom of the last fortnight is normal and

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reasonable but should not be taken too seriously. Consequently, when it becomes evident that her labor has started, she is pleased and not a little excited, and in that frame of mind communicates with her doctor or enters the maternity hospital.

In outlining the especial care which is necessary to obtain a physiologic labor, we must presume that all the accepted principles of good obstetrics are observed unless such principles cause emotional disturbance to a woman, in which case they should be applied in such a manner that no alarm is occasioned.

During the early stages of labor it is not necessary to keep a young woman in bed, providing that she understands how to behave when the uterus contracts. It is advisable for the attending physician to see his patient as early as possible in labor so that he can remind her of the teaching that she has had and point out to her the necessity for relaxation during contractions of the uterus. It is also an opportunity for reaffirming his confidence in her and thereby strengthening her confidence in him. At the same time it is his duty to see that her emotional attitude towards labor is sound; that she is not afraid to undertake a new and testing experience. There will be no necessity for him to stay with the patient once he has assured himself that she is capable of conducting herself satisfactorily—it is not usual that the physician need stay for more than fifteen or twenty minutes in the early stages of labor.

If, however, he wishes to stay so that he can watch all the phenomena of a normal labor and endeavor to deduce the significance of these phenomena, the picture presented to him will be very much as I propose to outline now. Unfortunately, it is not the custom to observe the phenomena of normal labor—it takes too much time, and the average scientist does prefer (and probably quite rightly) to observe abnormality rather than normality.

As the contractions continue to get a little stronger and possibly a little more frequent, so the manner of the patient gradually changes. The excited and easily laughing girl may become more serious, not because there is any undue strain placed on her, but because there are certain changes going on in her nature, probably the disposition of her blood sugar, but this has not been accurately worked out yet. The attendant must bear in mind that the first principle of his care is that the patient should not be allowed to have any anxiety or cause for anxiety, therefore his words, actions, and even his thoughts should be along lines of confidence and truth—you cannot deceive a woman in labor. She should already have become acquainted with the fundamentals upon which her own conduct must be based. She must be patient, self-controlled, and able to work when called upon. These cardinal principles upon which a woman conducts her own labor are very largely the cardinal principles upon which a woman will conduct her own life if she wishes to make a success of it, and this may be pointed out to her with advantage.

The first thing that will be noticed is that a succession of emotional phenomena, which are obviously correlated with the physical changes, occurs during the progress of labor. As the cervix dilates to about two-fifths, a woman becomes more conscious of the trial that she is undergoing; she recognizes that, although there is no discomfort attached to the contractions, she is being

subjected to the action of forces which are beyond her control. She is still quite happy, but between the contractions it will be noticed that she is quieter and more thoughtful. Frequently a flush over her malar bones is present.

As the hours of the first stage in the primiparous labor wear on, she will recognize the necessity for and the comfort which she gains from relaxation during the contractions; at the same time the demands upon her patience and her self-confidence increase. This is purely an emotional state in the large majority of women and has little or no relationship to physical pain. By the time the cervix is three-fifths dilated there is a necessity for advice and it is, what I term, *the first testing period* of labor. At this time a woman must not be left alone. She wants companionship; she wants the reiteration of the course of labor; she wants to be told what to do. She needs reassurance in a kindly but not over sympathetic manner—this is not a time for too much sympathy but rather for firm encouragement, common sense explanation, and companionship. Point out to her that this strain upon her fears and fancies is a normal part of labor which will soon pass, but on the other hand it is an indication of progress and nothing whatever to alarm her—it is indeed what we wish and what we expect.

Naturally these signs and symptoms vary a lot in different women, but it is unusual that a well-conducted woman will fail to reconstitute her ideas on labor at this point. The first testing point can be passed easily if treated with understanding of a woman's reactions and the influences to which her mind is being subjected. This is the time when deep medication or sedation is frequently employed because of failure to understand the significance of the emotional as well as the physical changes of a woman at this stage. Tiding over the "first test" is not a difficult matter. It can be done by a nursing sister or an assistant or anyone who is present to give the necessary comfort and advice. Not infrequently the husband proves to be an excellent attendant, and labor passes on satisfactorily until between four-fifths and full dilatation of the cervix. This is the *second testing period* of labor and it is not a purely emotional change. Owing to the nature of the sense receptors, the cervix uteri during full dilation may be subjected to a tension which gives rise to referred pain over the sacral area. This is described as a backache. The onset of this backache with the increased violence of contractions is frequently a stern test for a woman having her first child. My observations upon this phase are such that I have termed it the *pain period of labor,* and in the majority of physiologic labors it is the only time during which the woman has actual physical discomfort.

This is the time when the attendant obstetrician should be present with the woman. The diagnosis of four-fifths to full dilatation is made possible by close observation of the emotional changes in a woman and may be corroborated by examination. It is the *transition* from the first to the second stage, and if this is satisfactorily conducted the whole labor will take on a different character and have a best possible chance of becoming a physiologic function. Understanding and personal attention is again required. A woman needs hand pressure or rubbing over her sacrum to comfort her. She may

desire, during the contractions, a hand to hold; she may need a word of advice or a word of encouragement. This is variable in the different types of women that we have to deal with, but it must be recognized that this is the time above all others when an obstetric attendant should be present with the patient, for once this transition from the first to the second stage has been completed labor becomes a simple and interesting affair.

It is also at this time that a woman should be given an anesthetic should she require it. She should not be allowed to use the apparatus for self-induction. If she is given gas, trichlorethylene or gas and oxygen, the labor is in no way disturbed and there is no necessity to continue the anesthetic once she has assumed the second stage. If she finds the discomfort in her back more than she wishes to tolerate there is no reason why an injection of demerol (pethedin) should not be given, but the large majority of women will recognize that this discomfort is purely transient if they are told of it; they will agree and understand that the backache is not one which will increase, but one which will pass off, as indeed it does.

I frequently say "If, with help, you can put up with this for perhaps a dozen contractions, the backache will go, but I leave it to you to say whether you wish to have anything to relieve the discomfort or not." Most women say "No, it isn't as bad as all that but it feels as though its going to get much worse;" and that is one of the things about labor which must be carefully understood. So many of its sensations are threatening—they feel as if they are going to get very much worse, therefore they wake up in a woman's mind all the associations that she has of labor and all the fear-producing propaganda that has crossed her mind during her young adult life. Strict attention should be given to the breaking down of these fear-producing threatenings of discomfort during labor.

Once the second stage expulsive contractions are established, the woman changes entirely. She enjoys the effort that enables her to take some part; she is more than willing to admit that the passive patience of the first stage had become a great trial to her and now, "thank heavens," they say, "I can do something to help my baby into the world."

The early establishment of expulsive contractions can often be noticed when the woman takes a deep breath as she should when each contraction starts. The expiration will frequently be checkered or halted by a little laryngeal catch. It is quite involuntary, and it is the first indication of the establishment of expulsive contractions. Once that is heard she may be told to hold her breath "at the top" of the next contraction—she will understand from her own sensations what is meant by "at the top of." It is inadvisable to suggest that a woman pushes down or bears down at this stage—there is no advantage to be gained from it and she should be advised to follow the lead of her uterus and to change her routine from relaxation during the contractions as was necessary in the first stage, to relaxation between the contractions which is beneficial in the second stage.

At this time a woman should be told of the rupture of the bag of waters, for a sudden rush of fluid from below may be very alarming if unexpected.

She should also be instructed in the use of her analgesic apparatus, either Minnitts gas and oxygen or trichlorethylene inhaler, and it is placed within her reach to be used if she needs it.

When the second stage contractions have become well established and the head is advancing through the birth canal, the bearing down effort may be urged and increased. During the first stage the posture of the patient is of little importance, but in the second stage a definite posture must be assumed. After considerable experiment and trial the dorsal position has been found to have advantages over any other. One pillow under the shoulder blades and two pillows under the head and neck raises her upper back to an angle of about thirty degrees to the bed. With the onset of a contraction the knees are raised and held by the woman herself, with her hands either over the knees or in the popliteal spaces—the legs are widely separated. This is the posture of open squatting, but the body weight is taken on the lower back instead of on the feet.

With the onset of a contraction, the woman is warned to take two deep breaths and not to push until the uterus pushes for her. Then she holds her breath after a full inspiration and pushes down, takes a second breath, and again exerts an expulsive influence until the contraction wears off. She then puts her legs down, shuts her eyes, takes two or three more deep breaths and relaxes completely. In this way a marked stage of amnesia is induced between the contractions, and in a semi-conscious restfulness she will lie oblivious to her surroundings and her discriminatory and discretional senses will be lowered. Quiet peacefulness should reign in the labor ward, and noise of any sort must be avoided. Conversation should be eschewed unless the obstetrician wishes to advise or instruct her. This is best done immediately after a contraction, before she becomes completely relaxed again.

These periods of amnesic relaxation have two salutary influences upon labor. They ensure complete rest and maximum restitution of the hard-worked muscles, and by inhibiting sympathetic nerve impulses allow full and free circulation within the uterus so that a complete interchange of blood takes place, and the metabolites of muscular effort are not retained. The expulsive power of the uterine and skeletal muscles is thereby enhanced. Inertia or fatigue of a woman or her uterus rarely occur, and the necessity for forceps extraction consequently is minimized.

Careful observation should be made of the emotional changes of the second stage of labor. At first there is a revival of a woman's personality after the transition from the second testing period to the establishment of expulsive contractions. She will express relief and confidence and be alert to her surroundings, asking pertinent questions about the progress and duration of her labor. As the head passes deeply into the birth canal, the onset of amnesia, while relaxing between contractions, will be observed. In mid cavity a careless primitive self may appear. With the onset of a contraction a woman may tersely order her attendant to do this or that. A most docile and cultured person may say in commanding tones "Come on, another one—hurry up, hold my legs." They may give vent to expletives and belchings of no uncer-

tain quality with neither embarrassment nor apology. Such incidents are not remembered and often cannot be recalled after the child is born. A careless untidiness adds an element of drama which should not be mistaken for distress. But at this time care should be taken to detect the *third testing period* of labor.

When the occiput starts its rotation to the front and commences to exert direct pressure on the pelvic floor, the emotional state of a woman undergoes a sudden and sometimes violent change. It is an important phenomenon that is too frequently overlooked. A feeling of pressure is experienced which is alarming and intense, and the reaction is frequently one of exasperation leading to the expectancy of acute pain. It is the point at which the threat of pain is so real that women demand immediate relief, not for what is but for what they feel is imminent.

A woman obstetrician of wide experience discussed with me during the birth of her child all the phenomena I had recorded and the significance of them to her as a patient. Of this third testing period, she said, "It was the only time during labor that I was actually frightened because, although I was expecting these sensations, I had no idea they would be so intense." Although her sensations may have been intensified by severe injuries at a previous confinement, her observations are of importance.

Warn a woman, immediately this stage is detected in her behavior, that the feeling of pressure or even bursting through the rectum will not materialize. It is a further threat and will pass in two or three contractions. Ask her "Is it painful or does it threaten to be painful?" and advise her not to squeeze her anus up against it but to allow everything to go loose and bulge out below. Remind her that the anesthetic is by her side to use if she wishes. With the restoration of confidence the severity of the sensation speedily diminishes, and the bag of membranes, occiput, or caput succedaneum comes into view. If she is told that the head is visible her effort syndrome is restored and she again exerts herself to expel the child.

The facial expressions and grunts of a woman must not be mistaken for pain. The willingness to take an analgesic is a much better basis for the diagnosis of pain than the outward appearance that accompanies physical exertion and strain. The facial expressions of agony in athletes are not a demand for anesthesia, but evidence of unrestricted determination which, with victory, gives place to the exaltation of successful achievement. I frequently receive letters of complaint from women who have been forced to take an anesthetic by a sympathetic and misguided attendant who has mistaken their facial contortions and grunts for agony and so robbed them, in spite of their remonstrances, of the visible and tangible fruits of victory. A more careful understanding of the phenomena of the late second stage of labor and their true significance would prevent many disappointments and torn perineums, and not a few hurried low forceps deliveries.

As the head comes down on the perineum and the anus is dilated, its advance and retreat should be explained—for, as it slips back, a feeling of frustration and disappointment is experienced if this feature is not under-

stood. And finally, it remains down and crowns. This early crowning constitutes the *fourth* and final *testing period* of labor. The tightness and stretching is such that women feel they must split, and an instinctive protective resistance may result in an effort to tense the muscles of the outlet.

At this stage the knees should be kept up and not allowed to go down onto the bed again. They should be held at an angle just beyond ninety degrees to the bed, and the left leg held by an assistant. The right foot, if not supported by a second assistant, rests on the left hip of the attendant. The bearing down effort should be stopped. At this time a woman can breathe in and out and not hold her breath, allowing the unaided uterine effort to advance the head without violence. The patient should be kept under firm control, and after two or three contractions the vulval margin loses its sensitiveness, except at the upper quadrant by the clitoric folds. The extending head slowly lifts the occiput above the pubis.

A soft woollen pad should be held in the palm of the right hand to exert gentle pressure on the face and chin to prevent extension of the head before the pubis is well into the nape of the baby's neck. Lifting the chin is a sure way of tearing the perineum and it should be guided upward with the occipito mental line as closely as possible at right angles to the vulval orifice. In this way the smallest diameter of the head passes through the outlet, and many tears and episiotomies are avoided.

The delivery is not painful and the woman is frequently surprised to hear the first grumbling cry of her baby. The arms are freed, usually the posterior first but if an anterior hand presents, by passing the elbow across the infant's chest the arm may be delivered and the pressure on the perineum released. When both arms and shoulders are delivered and the cord is freed, the rotation of the shoulders should be completed by gently turning the child face to pubis while awaiting the next contraction. At this point it is my custom to wipe the baby's face and most mothers like to hold the hand of their child. There is no discomfort but rather elation and excitement. They demand to know its sex but are told that they must wait for the next contraction as its body is not fully born. The child is then delivered slowly and gently by carrying the body upward over the pubis.

After the cord has been separated, the infant is wrapped in a towel and handed immediately to its happy and delighted mother. Her emotional state is now that of pride and achievement—she is transfigured and appears to be a new and different person from the woman who, but a short time previously, labored for her child. As she takes her infant, a hand should be placed on the fundus of the uterus and it will be felt to go into a firm and prolonged contraction which is a manifestation of psychosomatic reaction. After a few minutes the child is placed in a warm cot and the woman is given a drink of hot glucose and water.

The third stage is explained and when the contractions of the uterus become strong enough for her to feel the desire to push down, or when the placenta is in the vagina, she is asked to give a long expulsive effort to squeeze out the spongy afterbirth.

TABLE I. STATISTICS OF 100 CONSECUTIVE DELIVERIES OF WOMEN ATTENDING THE "TRAINING FOR CHILDBIRTH" CLASSES AT A MATERNITY HOSPITAL IN THE MIDLANDS—WITH CONTROLS

	GROUP A (TRAINING CLASSES)	GROUP B (CONTROLS)
Average number of hours in labor	16 hr. 23 min.	20 hr. 26 min.
Average number of attendances at classes*	7.7	--
Forceps	9%	13%
Cesarean section	0%	1%
Drugs and analgesics	42%	98%
Analysis of above:		
Minnitts	5 cases	76 cases
Morphia and Hyocine	7 doses	29 doses
Mist 3 XVs	9 doses	25 doses
Heroin	17 doses	28 doses
Pitocin	3 doses	2 doses
General anesthetic	10 cases	16 cases
Nembutal	6 doses	6 doses
Pethidine	3 doses	3 doses
Pituitrin	2 doses	2 doses
Chocolate drops	1 dose	2 doses
Seconal	2 doses	1 dose
Chloral hydrate	1 dose	1 dose
Syrup of chloral	1 dose	3 doses

N. B. Drugs were never withheld in this GROUP A.

*Thirty-one cases attended over 10 times. The average time in labor for these is thirteen hours, forty-six minutes. It would therefore seem that there might be a case here for a *minimum* number of attendances (say 10) when arranging classes. The ideal is, of course, a weekly attendance throughout pregnancy.

TABLE II. COMPLICATIONS OF PREGNANCY

	GROUP A	GROUP B
Breech extraction and version 35/52	4	2
Monila vaginitis	1	0
Overdue—medical induction	10	15
E.U.A.—high head	2	4
Pre-eclampsia	5	5
A.P.H.	4	2
Hydramnios	1	0
Punctured membranes	2	9
Removal fibroid	1	0
Undiagnosed twins	1	(diagnosed) 1
Mitral stenosis	0	4
Chronic nephritis	0	1
Pleurisy and bronchitis	0	2
Anemia and hypertension	0	1

Such labors can be seen in the majority of healthy well-conducted women. There is rarely any hemorrhage, and seldom more than four to five ounces. Obstetric shock is not seen and lacerations are unusual. The well-being and happiness of the mother is impressive and the lusty health of the infant gratifying, for the major anxieties of labor are in the third stage and from these, in this way, the obstetrician may be protected.

It should be understood that no two labors are alike. They vary as widely as the natures of women. They are influenced by association, environment, and teaching. The experience and ability of the attendant is an important factor, for upon that the confidence and self-control of the woman depends to a large extent.

The four testing periods of labor vary in the intensity of their manifestation. Many women may give birth to a child without displaying a phase of

trial from beginning to end. Others are conscious only of the changes at the second testing period which is the most constant of all, whereas labors are attended in which all four testing periods present a demand for obstetric skill and understanding. When a phenomenon reoccurs from time to time throughout a series of physiologic labors, its significance should not be overlooked, for it is unlikely that a constantly recurring incident is devoid of importance.

It is obvious that these observations call for a much fuller understanding of the physiologic and chemical changes that occur in normal childbirth. In spite of the clinical advantages, so widely demonstrated by those who teach and practice natural methods, this approach is only in its infancy. When adequate investigation has been made it is likely that a more complete understanding of the normal will enable us to reduce the incidence of abnormality and morbidity in pregnancy, parturition, and puerperium.

TABLE III. COMPLICATIONS OF LABOR

	GROUP A	GROUP B
Fetal distress	7	1
ROL to ROP	1	1
Retained placenta	1	2
POP to brow	2	0
Face to pubes	1	0
Ruptured membranes and med. ind.	2	0
Secondary uterine inertia	1	1
Nipped anterior lip.	1	1
P.P.H.	1	0
Prolapsed arm and posterior	1	0
Disorderly uterine action	0	1
Low transverse arrest.	0	1

Column A in Tables I, II, and III gives 100 consecutive cases where women have attended the antenatal classes, and the physiotherapists have had full opportunity of being present throughout labor. All were booked patients.

Column B gives 100 women in the same age groups taken at random from the wards on the same day, where possible, as the delivery of the column A women. All were booked patients. Both columns concern *primiparas* only.

Only those women are included whose labors appeared to be likely to run a normal course when labor *started*. If labor became complicated later the case has been included.

These women were prepared by, but the labors were *not* conducted by, attendants familiar with the procedures for securing a physiologic childbirth.

Further information for details of the method may be found in the author's books: *Revelation of Childbirth* and *The Birth of a Child*, published in America by Harper and Brothers, New York.

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Craham, M.: The Effect of Radiation on Vaginal Cells in Cervical Carcinoma. I. Description of Cellular Changes. II. The Prognostic Significance, Surg., Gynec. & Obst. **84:** 166, 1947.

Two extremely significant papers are presented which discuss the effect of radiation therapy on vaginal cells as shown by the vaginal smear technique and the prognostic significance of this change in carcinoma of the cervix. In the first paper 206 cases of cervical carcinoma treated by radiation therapy were studied by this method. The changes seen in the cells were comparable in every respect to the irradiation changes seen in cervical biopsy in similar types of patients. The pyknosis and degeneration of nuclei, the swelling and vacuolization of cytoplasm, the evidence of abnormal mitoses and leucocytic infiltration with the formation of giant cells, are all seen in vaginal secretion just as they appear in cervical biopsies. The author points out that the vaginal smear method is a much simpler way of studying the reaction of both tumor and normal cells. It is often difficult to do serial biopsies on treated patients.

The second paper concerns the prognostic significance of these changes in 73 instances of cervical carcinoma. It is pointed out that there are two types of response as seen by the vaginal smear method. The good response shows a rather rapid disappearance of malignant cells and an equally rapid appearance of radiation change in the normal cells of the vaginal secretion. The poor response on the other hand shows neither a disappearance of malignant cells nor any marked radiation change in the normal cells. In the 73 cases studied, divisions into two groups, i.e., good and poor response to radiation, gave a prognostic accuracy of 88 per cent. While the follow-up of these cases is admittedly short and the series extremely small, nevertheless earlier work on cervical biopsy would seem to substantiate the claims made in this paper. If the method holds good after further study and longer follow-up, then it will give an excellent means for early prognosis as to the effect or lack of effect of radiation therapy.

L. M. HELLMAN.

Taylor, Howard C., Jr., and Becker, Walter F.: Carcinoma of the Corpus Uteri, Surg., Gynec. & Obst. **84:** 129, 1947.

This paper contains a review of 531 histologically verified cases of carcinoma of the body of the uterus which were admitted to Memorial Hospital during the period 1926 to 1940, inclusive. The total five-year cure rate was 38 per cent. There were 386 primary cases of which 39.9 per cent were alive and well in five years. If the patients who were lost track of when free from cancer, and those dying of intercurrent disease unrelated to carcinoma were subtracted, the five-year cure rate was approximately 45 per cent. There were 163 patients who received prior treatment for carcinoma of the body of the uterus, who were admitted to the Memorial Hospital during the fifteen years under consideration. Thirty of these patients presented no clinical evidence of carcinoma, and the diagnosis was confirmed only by reviewing the microscopic material from the institution in which they were originally treated. This group

of cases was designated as the prophylactic group. Twenty of the thirty patients were alive five years after first being seen, giving an absolute cure rate of 66.6 per cent. The remaining 133 patients were termed recurrent cases. They included many inoperable patients with fixed uteri and large abdominal masses. There were also recurrences in the vaginal vault and about the hymeneal ring and urethra. And finally, there was carcinoma of the cervical stump. There were 33 five-year cures in this group, giving an absolute cure rate of 24.8 per cent. The prognosis is determined by the gross extent of the disease and by the histologic type of carcinoma. The gross extent of the disease with its prognostic significance is as follows: dividing the five-year end results into five specified groups. Group 1, uterus not enlarged, 66 per cent salvage; Group 2 a, uterus not enlarged greater than a 2½-month gestation, 37.9 per cent; Group 3 a, carcinoma extending to the cervix, 24.3 per cent; and Group 3 b, carcinoma beyond the uterus, 11.2 per cent salvage. The tumors were also divided into histologic types for the purpose of prognosis, grades 1 and 2 giving a 47.2 per cent salvage, grades 3 and 4 giving a 22.8 per cent salvage and adenoacanthoma giving a 51.3 per cent salvage. No true evaluation of the difference between operative and radiation therapy could be made because of the fact that there were more cases in the radiation group and, in the main, these also were the more severely ill. Neither could the question of cure rate from hysterectomy with or without radiation be solved.

L. M. HELLMAN.

Buschke, Franz, and Cantril, Simeon T.: Treatment of Carcinoma of the Uterine Cervix, West. J. Surg. **55:** 152, 1947.

The evolution of radiation therapy in the treatment of carcinoma of the cervix is reviewed. The basic principles of treatment used by the author are those of the Curie Institute originally described by Regaud and his co-workers. The vaginal applicators used for treatment are those developed at the Holt Radium Institute in Manchester, England. Minute attention is given to the details of anatomic distribution of the radium. In all cases, except Stage 1, the radium is followed by roentgen therapy. Rectal and bladder complications are more frequent if roentgen therapy precedes the radium therapy.

The results of treatment are as follows, based on the five-year cure rate:

Stage 1—83%
Stage 2—56%
Stage 3—38%

WILLIAM BICKERS.

Halberstaedter, L., and Hochman, A.: The Artificial Menopause and Cancer of the Breast, J. A. M. A. **131:** 810, 1946.

The authors review extensively the literature of artificial menopause in cancer of the breast both in human beings and in experimental animals. The authors treated 60 women suffering from cancer of the breast and its metastases by producing artificial menopause with x-radiation of the ovaries. Thirty-four women, or 56 per cent, benefited from this treatment. The improvement due to the interruption of estrogenic secretion is of short duration, since vicarious estrogenic secretion from other sources than the ovaries intervenes. Typical adenocarcinomas are more susceptible than anaplastic cancer of the breast due to the estrogen-inhibiting influence of the artificial menopause.

WILLIAM BERMAN.

Black, B. Marden, and Howe, Rulon F.: Primary Carcinomas of the Breasts, Uterus and Colon, Proc. Staff Meet. Mayo Clin. **21:** 484, 1946.

Multiple primary malignant lesions have been found most frequently at autopsy, and their differentiation from recurrent or metastatic malignant lesions has been based on pathological rather than on clinical findings. The clinical diagnosis of multiple primary malignant lesions has been more difficult to establish.

In the case reported the patient was first seen at the Mayo Clinic in July, 1939; she came to the hospital within a few days after her physician had discovered a small nodule

in the right breast. A radical mastectomy was done and the tumor was found to be an adenocarcinoma grade 2; there was no involvement of the regional lymph nodes, but postoperative roentgen therapy was employed. Two years later, in June, 1941, a small tumor was found in the left breast on routine examination. In the area of the radical mastectomy on the right side there was no evidence of local or regional recurrence. A left radical mastectomy was done; the tumor was found to be an adenocarcinoma, grade 4, with no evidence of lymph node involvement. The patient was in good health until May, 1943, when her menstrual flow increased in amount; and in the next six months the menorrhagia became continuous, so that in November, 1943, a total hysterectomy was done at another hospital. An adenocarcinoma, grade 1, of the fundus of the uterus was found. This diagnosis was confirmed by examinations of sections of the malignant tissue at the Clinic. The patient was again admitted to the Clinic in October, 1945. For a year she had noted a mass in the right quadrant of the abdomen, and in the last few months had had cramping abdominal pains and constipation, with considerable loss of weight. A diagnosis of carcinoma of the ascending colon was made on x-ray examination. Radical resection with a side-to-side ileocolostomy was done. The tumor was found to be an adenocarcinoma, grade 2, which had involved the regional lymph nodes. The carcinomas in this case fulfilled Goetze's criteria for multiple primary malignant lesions.

The authors suggest that with earlier recognition and improved treatment of carcinoma of various types, more patients will survive the treatment of one neoplasm for long periods and that it seems probable that a larger number of cases of multiple primary carcinoma will be recognized. The necessity for the careful follow-up of cancer patients is evident.

HARVEY B. MATTHEWS.

Endocrinology

Breteche, M.: Hypothyroidal Cervicitis, Compt. rend. Soc. Franc. de Gynec. **26**: 114, 1946.

Breteche, in his study of a case of one-child sterility, in a 25-year-old woman, observed a correlation of hypothyroid state and refractive cervicitis resistant to local therapy. Repeated coagulations of the cervix, sulfonamides, and other therapy failed to clear up this condition. However, because of a nodular goiter and a gradually developing hyperthyroid state with cardiac and ocular symptoms, the basal metabolism rate changing from -11 to a +18, a hemithyroidectomy was done. The basal metabolism rates then fluctuated from a -25 to -59 per cent, necessitating thyroid extract. As long as the thyroid was administered the cervicitis and "erosion" disappeared. A reduction of the thyroid reproduced cervical symptoms. Incidentally, the patient became pregnant twice, delivering two normal children.

Because of the above cases the writer reviewed 263 cervicitis cases. He found that 226 (86 per cent) of these cases were upon an infectious basis; that 21 cases, or 8 per cent, were indisputably upon the basis of hypothyroidism, while the remaining 16 cases, 6 per cent, may possibly have been associated with deficiency in thyroid function. C. E. FOLSOME.

Endometriosis

Teilum, Gunnar: Carcinoma Arising in Ovarian Endometriosis, Acta obst. et gynec. Scandinav. **25**: 377, 1945.

Teilum reports a case of adenocarcinoma in the ovary of a 42-year-old woman, with histologically reliable and demonstrable *anlage* suggesting certainty of origin, in his opinion, from the mucosa of a typical chocolate cyst. Upon the inner wall of the cyst were found multicentrically developed papillomatous tumor tissue ingrowing into the cyst wall. In other areas he was able to demonstrate a transition from the normal endometrial epithelium to tumor. Endometriosis, without malignancy, was demonstrable in the opposite ovary. The uterus exhibited slight polypoid hyperplasia of the endometrium. C. E. FOLSOME.

Mm. Masse, Traissac and Dax: Treatment of Endometriosis of the Rectovaginal Septum by Implantation of Testosterone Pellets, Compt. rend. Soc. Franc. de Gynec. **26:** 105, 1946.

The authors, discouraged by necessity of frequent injections of testosterone propionate necessary to control the pain of endometrious, decided to implant pellets of this drug to overcome this problem. In two cases the authors implanted such pellets; 200 mg. and 300 mg. in the respective instances.

In the first case, a woman, aged 40 years, gave a history of menorrhagia, polymenorrhea, severe dysmenorrhea associated with perineal radiating pains. Clinically there were present two nodules the size of small hazelnuts with smaller areas of endometrius of the cul-de-sac and rectovaginal septum. Intramuscular injections of testosterone, 100 mg. per month, gave but minimal relief of pain. In February, 1946, a 200 mg. pellet was implanted. The effect was immediate, menses became regular, perineal pain disappeared, and, while the nodulation of the involved areas could be felt, they were no longer painful.

The second case was a 44-year-old woman submitting a history of dysmenorrhea of increasing severity and associated for six months with rectal tenesmus. A chocolate cyst was removed through laparotomy at which time rather rectovaginal endometriosus was discovered. Ten days later a 300 mg. testosterone propionate pellet was implanted. Since that time the menses recurred regularly and without pain. C. E. FOLSOME.

Gynecology

Arostegui, Gonzalo E., and Blanco, F. Leon: Brenner Cell Tumors of the Ovary: A Literature Review and Presentation of Three Cases, Rev. cubana de obst. y ginec. **7:** 27, 1945.

The authors review the literature on the topic of Brenner cell tumors of the ovary as evaluated from 84 references. They add three new cases of their own to the medical writings. Their patients were aged 33, 34, and 60 years, respectively. In all instances the tumors in their series were unilateral and localized in each case in the right ovary. Grossly the tumors varied in size, viz.: (1) 4 by 3 by 2 cm., (2) 12 by 10 by 5 cm., and (3) 5 cm. in diameter. Histologically, they were all classed as Brenner cell tumors of Meyer's Group A.
C. E. FOLSOME.

Shaw, H. N., and Gaspar, John: Chronic Salpingitis, West. J. Surg. **55:** 81, 1947.

An attempt is made to evaluate sulfonamide therapy in the treatment of acute pelvic inflammatory disease. It could not be demonstrated that resolution of the inflammatory process proceeded more rapidly when sulfonamides were added to the usual supportive treatment. Management of this condition at the Los Angeles County General Hospital now is limited to bed rest, adequate diet and the sulfonamides only in very acute cases without pelvic masses. The white blood cell count and sedimentation rate are held to be rather accurate indices of the degree of inflammatory activity.

The presence of inflammatory masses persisting after adequate conservative treatment is considered an indication for operation. Deep cautery of the cervix always precedes operation and, where the inflammatory process is extensive, the removal of both tubes, both ovaries, and the uterus is indicated. In cases where purulent material is spilled, 5 to 8 Gm. of sulfonimide crystals are left in the peritoneal cavity. The appendix should be removed as routine.

There were 11 deaths in these 759 patients who comprised this study. Two of these deaths resulted from advanced pelvic tuberculosis. Seven patients died of peritonitis with or without obstruction. One patient died from peritonitis originating in a cervical stump abscess. Perhaps she could have been saved with proper drainage.

WILLIAM BICKERS.

Gynecologic Operations

Sardina, M. C. D., and Revilla y Aguda, J. M.: Cervicocervical Fistula, Rev. cubana de obst. y ginec. **7**: 55, 1945.

The authors report an unusual case of cervicocervical fistula occurring in a 42-year-old patient. The patient had suffered a rectovaginal fistula following her first pregnancy delivered by forceps. Fifteen months later she experienced an incomplete abortion requiring a curettage to remove incomplete products of conception. An incidental appendectomy was done fifteen days later. For the next seventeen years the patient was troubled with leucorrhea, later on with menorrhagia and severe secondary dysmenorrhea. The later symptoms indicated a panhysterectomy, which was done. Preoperative hysterosalpingography had demonstrated the rare fistula tract which was confirmed upon operation. Final pathologic diagnosis was chronic cervicitis with posttraumatic cervicocervical fistula. C. E. FOLSOME.

Labor

Dennen, Edward H.: The Selection of an Obstetric Forceps to Suit the Case, Virginia M. Monthly **150**: April, 1947.

The author advocates the use of a large variety of forceps for particular obstetrical indications. For occiput anterior position on the perineum many types of instrument will satisfy the requirements. With a low pubic arch he prefers a forceps with a good pelvic curve. The Simpson, Elliott, or Tucker-McLane instruments are recommended. For occiput anterior above the pelvic outlet a fixed axis traction forcep is preferred. In the posterior occiput, Kielland forceps are preferred to the Scanzoni maneuver. The only exception is in the anthropoid pelvis where rotation is difficult and here delivery as a posterior occiput is preferred. For aftercoming heads in breech extractions the Piper forceps finds an important place. A high transverse head with posterior parietal presentation requires the Barton forceps. WILLIAM BICKERS.

Paruianen, Sakari, and Pärnänen: Obstetrical and Puerperal Diseases Causing Mortality in Finland, Acta obst. et gynec. Scandinav. **26**: 1-72, 1946.

The authors, from the First and Third Women's Clinic, Helsinki, review statistical maternal mortality data obtained from the Central Statistical Office of Finland and compare it to these findings of the mortality records in their clinics. There were 185,363 deaths in Finland during the years 1936 to 1943, inclusive, and in this period 2,562 women died of diseases of pregnancy, childbirth, or the puerperal state, an incidence of 1.39 per cent. In the same period were 593,250 pregnancies and 1,727 deaths in childbirth, a ratio of 345 births to each maternal death.

At the two clinics mentioned above, 221 women died of obstetric or puerperal causes during the years 1935 to 1944.

The death rate in diseases of pregnancy, childbirth, and the puerperal state was on an average 1.39 per cent of the total death rate of women in Finland, 6.35 per cent of the death rate of 15- to 49-year-old women, and 10.1 per cent of the death rate of 30- to 34-year-old women. The mortality rate is steadily decreasing. While 79.7 per cent of the total population live in the country, 73.1 per cent of deaths were from rural districts. Twenty-three per cent of the deaths were single women, 66.6 per cent died in hospitals, 12.9 per cent died under treatment at home, and 20.5 per cent were not treated.

Abortions accounted for 28.9 per cent of the maternal deaths. In these abortion cases 93.0 per cent were septic and criminal, with 48.6 per cent occurring among the town population, and 52.7 per cent among the unwed mothers. The hospital abortion death rate was 3.1 per cent (5,113 abortions, 159 deaths). There has been a rapid increase in the number of abortions, being seven times greater in the hospital series. It is calculated that about 300,000 abortions took place in Finland between 1936 and 1943.

The authors consider abortion their most burning and social problem. Fifty-seven per cent of the deaths were in women under 30 years of age, and, more important, the writers estimate that associated inflammatory disease causes illness, invalidism, or sterility in over 10,000 cases yearly. While the sequelae can be treated, the causes are social and possibly legal. The causes should be considered as diseases of the nation.

Deaths in childbirth have reduced steadily since 1751; in the years 1936 to 1943 the rate was 0.29 per cent. In Helsinki University Hospital the direct deaths of childbirth were 0.28 per cent (19,965 births, 48 deaths)—divided as follows: 84.4 per cent of deaths were from country districts, 15.6 per cent were urban origin, and 13.0 per cent were unmarried. Only 32.4 per cent of the maternity cases could be admitted to the hospital because of lack of bed space.

The major causes of obstetric death in Finland include 461 cases of toxemias of pregnancy; 595 cases of puerperal sepsis; 199 other hemorrhages; 93 morbid states; 129 puerperal emboli; 78 placenta previa; 68 dystocia; and 49 cases of ruptured uteri. Septicemia has entirely disappeared from the hospital series after 1941, but toxemias are increasing in frequency.

In the hospital series (19,965 births and 48 deaths) cesarean section death rate was 5.4 per cent (31.0 per cent eclampsia mortality), while 46.0 per cent of cesarean deaths were attributed to heart failure.

The authors conclude that the most important means of decreasing childbirth mortality is prophylaxis. The text is illustrated by 13 well documented tables. C. E. FOLSOME.

Beclere, Claude, and Simonnet, H.: Postpartum Amenorrhea Due to Secondary Hypophyseal Insufficiency and Its Treatment, Presse méd. 12: 175-177, 1946.

The authors have described in previous articles two principal types of amenorrhea, the hypohormonal and the hyperhormonal. A third type, that which occurs post partum, is now discussed on the basis of their experience with eighteen cases treated by the administration of gonadotrophins. Three of these patients had experienced amenorrhea for twelve, nine, and eight years, respectively. The physical examinations of these eighteen patients revealed atrophy of the uterus in each case. The history in fourteen of the eighteen patients revealed previous menstrual irregularities, late onset of the menses, previous episodes of amenorrhea, and variations from normal in amount and interval.

Laboratory examinations revealed gonadotrophins present in amounts less than 10 mouse units and estrogens present in amounts less than 100 international units which the authors state would indicate primarily a hypophyseal insufficiency and secondarily an ovarian failure. This secondary hypophyseal failure has an abrupt onset as a result of the pregnancy. The authors state that the evidence points to increase in function of the hypophysis early in pregnancy and diminishing function in the end of pregnancy. The enormous hormonal production by the placenta probably inhibits the gonadotropic secretion by the hypophysis. It was felt that the levels of gonadotrophins and the absence of vasomotor waves excluded menopause praecox as a cause of amenorrhea in these cases of postpartum amenorrhea.

The eighteen cases were treated by injection of gonadotrophins alone with success in fifteen cases. One other patient was given estrogens and progesterone in addition and menstruation occurred. In only two cases was treatment unsuccessful. The authors state that postpartum amenorrhea of the type herein described is the instance of hypophyseal insufficiency where gonadotrophins alone are indicated. L. M. RANDALL.

Miscellaneous

Lubinski, H. H., and Portnuff, J. C.: The Influence of Heat and Formalin Upon the Rh Agglutinogen, J. Lab. & Clin. Med. 32: 178, 1947.

A differential sensitivity of agglutinogens to heat and formalin is demonstrated. The authors have shown that heating destroys the reactivity of Rh agglutinogen to both anti-Rh

and anti-Rh blocking sera, while the A, B, M, and N agglutinogens do not lose their reactivity to their respective anti-sera under similar conditions. Treatment with formalin evokes a similar differential response, but to a lesser degree.

The authors mention variation in location in the cell, chemical structure, or quantitative differences as possible explanations for these observed phenomena. S. B. GUSBERG.

Sperling, Gladys A., Loosli, J. K., Barnes, L. L., and McCay, Clive M.: The Effect of Coffee, Human Diets, and Inheritance Upon the Life Span of Rats, J. Gerontology **1:** 426, 1946.

Three diets were fed to groups of eighty rats throughout life. One diet resembled that eaten by many persons in northeastern United States. A second diet was similar to this but supposedly better because of the inclusion of more whole wheat bread, milk, and liver. A third was supplemented with vitamins. Each diet was fed with and without a moderate supplement of coffee, equal to about a cup per person per day. Life span data afforded no evidence for the superiority of any of the three diets. Coffee at this low level was not injurious and may have had a favorable effect upon the survival of the females. An auxiliary study in which coffee was fed as the sole source of fluid during lactation and the growth of three generations afforded additional evidence that even large amounts exerted no unfavorable effect. Evidence is presented that inheritance exerts a definite influence upon the length of life of the white rat. EDWARD C. HUGHES.

Davenport, J. W., Jr.: The Prevention of Rh Isoimmunization Due to Blood Transfusion, New Orleans M. & S. J. **99:** 376, 1947.

The prevention of Rh isoimmunization is a responsibility which the medical profession must assume and this is particularly true as regards the female. Of the total female population, 15 per cent are Rh negative. The transfusion of these females with Rh-positive blood will result in immunization in approximately one-half of them. It is imperative that routine typing include little girls and infants who are to be transfused. Transfusion of these individuals with Rh-positive blood will immunize many of them to the point where in subsequent marriage to an Rh-positive male they will be subjected to the possibility of giving birth to erythroblastotic infants. Since there is no way of de-immunizing an Rh-negative female already immunized by Rh-positive transfusions, her reproductive potential is nil.

Regarding male patients, the problem arises only in relationship to multiple transfusions. WILLIAM BICKERS.

Meigs, Joe V.: The Vaginal Smear, J. A. M. A. **133:** 75, 1947.

The author reports 2,749 cases of vaginal smear with an error of only 3.3 per cent. It is obvious that this method is of extreme value in enabling the physician, if not to make a definite diagnosis, at least to screen satisfactorily women who come for routine examination. A positive smear indicates that careful further studies both by smear and by biopsy are indicated. The author has rarely allowed a positive vaginal smear to be the sole reason for radical surgery. The individual cell is the most important feature of the vaginal smear technique. The nucleus of the cell is the main diagnostic criterion. The cancer cell has a large abnormal nucleus and in groups a variation in size and shape is obvious. It is important to note the paucity of cytoplasm as compared to the amount seen in the normal cell. The ratio of nucleus to cytoplasm is different in the cancer cell from that in the normal cell. In cancer of the endometrium the same criteria are true, but there is less variation in the size and shape of the nucleus, yet the difference is real after cytological criteria for diagnosis are given.

It is difficult to explain the finding of a positive smear and a negative biopsy. The number of errors of false positive smears has been 2 per cent. In 3.5 per cent of the cases of cervical cancer in which the slides were called negative, reobservation still did not show

signs of tumor cells on the slides. In cancer of the endometrium the diagnosis is somewhat more difficult. The error of correct diagnosis is about 2 per cent. A number of cases of diagnosis of cancer by vaginal smear are quoted. WILLIAM BERMAN.

Newborn

Bush, J. A. Kyle, Lenox, Cora C., and Myers, Hu C.: Volvulus Neonatorum, South. Surgeon **13:** 204, 1947.

Volvulus neonatorum is caused by certain factors resulting from abnormal embryologic development. Incomplete rotation upon the superior mesenteric artery or failure in the complete degeneration of the yolk stalk may produce anatomical changes contributing to the development of volvulus. A case is reported in the newborn; the infant was seen six days after birth at which time persistent vomiting had resulted in dehydration and icterus. X-ray examination revealed obstruction in the duodenum. The infant was treated by a nasal tube and injections of fluids, and operated upon on the tenth day of life. The mesentery was found rotated through one complete circle with resulting obstruction at numerous points in the small intestine. Obstruction was relieved by uncoiling the intestine and placing the mesentery in proper relation to it. The patient recovered. WILLIAM BICKERS.

Weymuller, Charles A., Beck, Alfred C., and Ittner, Elizabeth J.: Measures for the Protection of Newborn Infants, J. A. M. A. **133:** 78, 1947.

The authors mention three circumstances that favor the common type of nursery infections.

1. Unnecessary contact with visitors, nurses and physicians.
2. Inadequate isolation of the infants from one another in the nursery.
3. Faulty technique for preventing the spread of contamination.

Certain corrective changes in the visiting hours, nursing and doctors' technique in the handling of babies, and the supervision of ward maids and cleaning women are made. Every nursery unit has its own complete examining room. The architecture of the nurseries is such as to prevent crowding. Nursing assignments are such as to permit one nurse to care for eight babies and one premature only. She has complete care of those babies. The formula room is completely removed from the hospital section containing the nurseries and sick patients.

Nurses are carefully supervised and inspected and are relieved of duty immediately when ill. Their throats are cultured when they start on duty and whenever it is indicated while on duty. Numerous other precautionary measures in the nurseries are mentioned.

The authors report excellent results in their prophylactic anointment of newborn infants with 15 Gm. of 5 per cent sulfathiazole ointment. As a result of the war and nursing shortage an epidemic of diarrhea occurred in October, 1945, and affected 19 infants. All of them recovered. WILLIAM BERMAN.

Correspondence

Advanced Age for Childbirth

To the Editor.—The birth of the twenty-seventh child to a 65-year-old Negro woman was publicized both in the lay press, September, 1946, and in the *Journal of the American Medical Association.* This publicity has resulted in many inquiries to this clinic for verification. The present letter summarizes the case as well as the efforts made to establish the patient's true age.

The patient, Mrs. M. J., entered the Prenatal Clinic of the Ohio State University Hospital in July, 1946. She purported to be gravida xxi, para xxvi, and stated that she was 65 years of age. Her last menstrual period was March 22, 1946, but she gave a history of menses the first few months of each previous pregnancy. Menses had started at the age of 13 years, the patient had a 28-day cycle and flowed three to five days with no unusual blood loss with her periods. Fetal movement was first noticed April 5, 1946.

Physical examination revealed an obese Negro woman; weight 284 pounds; height 5 feet 2¾ inches. Patient did not appear to be her stated age of 65 years, but looked to be approximately 45 years of age. No fetal heart was heard; Chadwick's and Hegar's sign were positive; ballotment was present. Pelvimetry indicated a gynoid pelvis. X-ray report: single fetus, cephalic presentation, adequate pelvis. The remainder of the prenatal course was uneventful, and a living female was delivered spontaneously, Sept. 26, 1946.

A review of the patient's obstetric history reveals that she had six sets of twins and 15 single children. She had been married twice. Her first husband was killed in a mine accident in Greensboro, N. C., in 1913. The second husband is a resident of this city and is 60 years of age.

Verification of an individual's age is not always easy. This patient's claim rests chiefly upon her birth date as recorded in her family Bible. The date of birth is given as April 5, 1881, and her maiden name is recorded as Mary Matilda Walker. A photostatic copy of this Bible record was obtained in the course of efforts to establish her actual age.

The patient referred the writer to a white family of this city with whom she had had long contact. The oldest living member of this family, an insurance agent, aged 35 years, was willing to sign a certified statement to the effect that the patient had worked as a cook for his grandfather in Hickory, N. C. This man further stated that to the best of his memory the patient's present professed age coincides with that she gave when she was in his grandfather's employ. An attempt to verify the marriage and subsequent death of the first husband was unsuccessful. The Recorder of Deeds in Greensboro, N. C., reported that no vital statistics were kept in North Carolina before 1913.

A systematic review of the birth certificates of the patient's children, however, revealed a marked discrepancy. In March, 1927, the patient delivered twins whose births are recorded at the Bureau of Vital Statistics. On these birth certificates the mother's age is given as 27, which would make her age, at present, 48. It is then noted that the ages for the mother in subsequent births are not chronologic. In 1928, her age was given as 43; in 1930, 44; in 1936, 55; and in 1942, 61. Scrutiny of the initial birth certificate on file in Columbus, Ohio, shows that this patient then (in 1927) reported six previous children. It would seem, therefore, that this patient had six children by her first marriage rather than the purported 14.

It is the opinion of the writer that the wide variety of ages which the patient gave in recording the births of previous children, and particularly her rapid "aging" in the last few of these birth certificates mitigates against the acceptance of her stated age. The fact that the earliest birth certificate we are able to obtain records six previous children born to this mother instead of 14, the number she states were born prior to coming to this community, also casts doubt on her story. It is not felt, on the basis of the investigation to date, that this can be accepted as a delivery at an advanced age.

JOHN H. HOLZAEPFEL, M.D.

COLUMBUS, OHIO
July 22, 1947.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year.

A number of changes in Board regulations and requirements were put into effect at the last annual meeting of the Board held in Pittsburgh, Pa., from June 1 to June 7, 1947. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months regardless of the duration of the course.

Applications are now being received for the 1948 examinations. Closing date for these applications will be Nov. 1, 1947.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Emil Novak, Baltimore, Md. *Secretary,* Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* A. D. Campbell, Montreal, Quebec. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* J. Randolph Perdue, Miami, Fla. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* William F. Mengert, Dallas, Texas. *Secretary,* A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.

New York Obstetrical Society. (1863) *President,* Albert H. Aldridge. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* John B. Montgomery. *Secretary,* James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Aaron E. Kanter. *Secretary,* Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Alexander E. Dunbar. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Carroll J. Fairo. *Secretary,* Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Samuel S. Gordon. *Secretary,* J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Charles J. Barone. *Secretary,* Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* Frederick J. Lynch. *Secretary,* Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Henry N. Shaw. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.

Washington Gynecological Society. (1933) *President,* Lawrence Lee Cockerille. *Secretary,* Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Dr. Earl Conway Smith. *Secretary,* John S. Herring, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.

St. Louis Gynecological Society. (1924) *President,* Otto Krebs. *Secretary,* John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Clarence E. Toshach. *Secretary,* John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Raymond J. Pieri. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Carl M. Helwig. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* J. M. Freeman. *Secretary-Treasurer,* Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* S. E. Oglesby. *Secretary,* L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Wynne M. Silbernagel. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Austin B. Johnson. *Secretary,* Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* George Muscillo. *Secretary,* Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima, Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Thomas J. Sims. *Secretary,* LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Carl E. Krugmeier. *Secretary-Treasurer,* A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.

Akron Obstetrical and Gynecological Society. (1946) *President,* L. L. Bottsford. *Secretary-Treasurer,* N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.

Minnesota Society of Obstetrics and Gynecology. *President,* L. M. Randall. *Secretary,* Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* M. C. Wilson. *Secretary,* George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* M. E. Grier. *Secretary,* B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Le Roy H. Sadler. *Secretary-Treasurer,* John W. Records, 301 Northwest 12 Street, Oklahoma City.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* Robert E. Faulkner. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.